

**Synthetic Studies Towards The Marine
Natural Product Phorboxazole A**

by

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DECLARATION

I declare that the substance of this thesis has not been submitted, nor is concurrently being submitted in candidature for any other degree. I also declare that the work embodied in this thesis is the result of my own investigations. Where the work of other investigators has been used, this has been fully acknowledged in the text.

J. A. Tornos

G. Pattenden

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Finally I would like to thank all my family and friends for their continued support throughout the last three years.

ABSTRACT

The thesis describes synthetic studies towards the marine natural product phorboxazole A. This unprecedented compound was recently isolated from an Indian Ocean sponge and displays extraordinary levels of cytostatic activity against a broad range of human cancer cell lines. The Introduction summarises a variety of different natural products which have been targeted as anti-cancer agents, and compares their mode of action with that of phorboxazole A. A review of structurally related natural products is then included, followed by an account of how phorboxazole A was isolated and its structure determined. The Introduction concludes with a brief discussion on our planned retrosynthetic analysis and contemporaneous studies within our research group towards phorboxazole A.

The Results and Discussion section of the thesis contains details of our synthetic studies towards two of the key fragments present from our retrosynthetic analysis, namely the oxazole *bis*-pyran unit and the side chain. A detailed discussion is presented throughout this section including a review of the hetero Diels-Alder reaction and methods of oxazole formation. This section culminates with a successful synthesis of the entire side chain of phorboxazole A.

The third chapter of the thesis is the Experimental section containing full details of the preparative work completed and listing spectroscopic and analytical data for all new compounds synthesised during the study.

The thesis is concluded by a schematic account of the contemporaneous total synthesis of phorboxazole A by the Forsyth research group at the University of Minnesota.

ABBREVIATIONS

Ac	acetyl
AIBN	azo <i>bis</i> (isobutyronitrile)
Ar	aryl
BINOL	binaphthol
Bn	benzyl
BOC	<i>tert</i> -butyloxycarbonyl
Bu	butyl
Cp	cyclopentadiene
CAN	ceric ammonium nitrate
CSA	10-camphorsulfonic acid
DAST	diethylaminosulfur trifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DIBAL-H	di- <i>isobutyl</i> aluminium hydride
DIAD	di- <i>isopropyl</i> azodicarboxylate
DIPEA	di- <i>isopropyl</i> ethylamine
DMAP	4-dimethylaminopyridine
DMF	<i>N, N</i> -dimethylformamide
2,2-DMP	2,2-dimethoxypropane
DMSO	dimethylsulfoxide
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
ee	enantiomeric excess

Et	ethyl
HMPA	hexamethylphosphoramide
HMTA	hexamethylphosphorus triamide
HOBT	1-hydroxybenzotriazole hydrate
Im	imidazole
ipc	isopinocampheyl
IR	infra red
KHMDS	potassium <i>bis</i> -(trimethylsilyl)amide
LDA	lithium di- <i>isopropyl</i> amide
LiHMDS	lithium <i>bis</i> -(trimethylsilyl)amide
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
Ms	methane sulfonyl
NBS	<i>N</i> -bromosuccinimide
NaHMDS	sodium <i>bis</i> -(trimethylsilyl)amide
NMM	4-methylmorpholine
NMO	4-methylmorpholine- <i>N</i> -oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PMB	<i>para</i> -methoxybenzyl
PNBA	<i>para</i> -nitrobenzyl alcohol
PPTS	pyridinium <i>para</i> -toluenesulfonate
Pr	propyl
PTSA	<i>para</i> -toluenesulfonic acid
Py	pyridine
pyBOP	(benzotriazol-1-yloxy-tripyrrolidino)phosphonium hexafluorophosphate

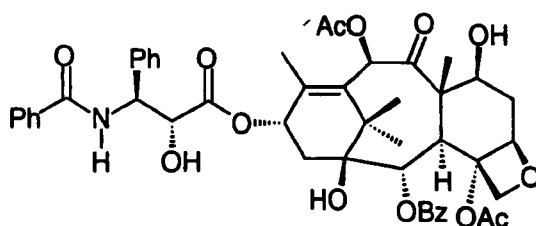
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBHP	<i>tert</i> -butylhydroperoxide
TBS / TBDMS	<i>tert</i> -butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethane sulfonate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
tlc	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetra- <i>n</i> -propylammonium perruthenate
TPS / TBDPS	<i>tert</i> -butyldiphenylsilyl
Ts	<i>para</i> -toluenesulfonyl
UV	ultraviolet

1. INTRODUCTION

1.1 The Quest for a New Anti-Cancer Agent

Cancer, in all its forms, has become one of the most significant causes of mortality in the human species. It is estimated that over six million new incidences world-wide will be reported during the forthcoming year. In the United Kingdom alone, cancer accounts for a quarter of all deaths, and in 1995 this equated to 160, 000 people, from which almost a quarter were attributed to lung cancer.¹

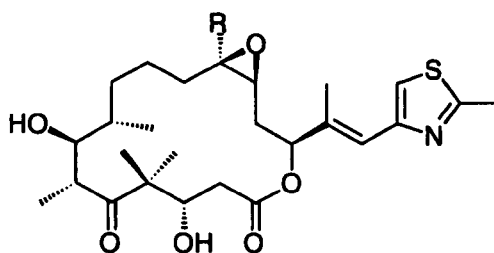
Horrrifying statistics such as these have led scientists to research the causes of cancer and attempt to provide cures. The search for anti-tumour compounds to combat this disease has been intense. Scientists have often turned to Nature for 'inspiration' and 'answers' to the 'questions' posed by cancer. Following the initiation of a screening program for anti-tumour agents from the plant kingdom by the United States National Cancer Institute (NCI) in 1961, the complex diterpene Taxol™ (paclitaxel) (1) was discovered in 1971, isolated from the bark of the Pacific Yew tree, *Taxus brevifolia*.² But it was not until 1979 when taxol's mode of action was discovered that it was considered as a candidate for development.³ Taxol has taken up a major share of the anti-cancer market and become a billion dollar drug. Developed by Bristol-Myers Squibb, and currently available in more than sixty countries, taxol is used mainly for the treatment of a variety of solid tumours, commonly encountered with ovarian and breast cancer.



1 Taxol

Since the discovery of taxol (1), medicinal chemists have continued to regard natural products as an excellent starting point in the search for lead compounds for drug development. The downside to taxol is its scarcity, its highly complex structure and, also its low aqueous solubility.⁴ Thus, the search for a more superior anti-tumoural agent has always been of high priority.

In the early 1990s a new chapter in this quest began to unfold, with the isolation of the cytotoxic agents epothilone A (2) and B (3), by Hofle *et al.*⁵ Two independent groups of scientists determined that the epothilones had a similar mechanism of action to taxol and were competitive inhibitors of [³H]taxol binding with almost identical IC₅₀ values to that of taxol.^{5b,6} It was these observations that stimulated great excitement from the chemical community, and led to a flurry of activity towards the total synthesis of the epothilones. Due to their much simplified structure, compared to that of taxol and the ability to make analogues many research groups have since reported the total synthesis of the epothilones,⁷ with some of the leading groups in the field developing extensive libraries and analogues for full biological evaluation and structure activity relationship (SAR) studies.^{8,9}

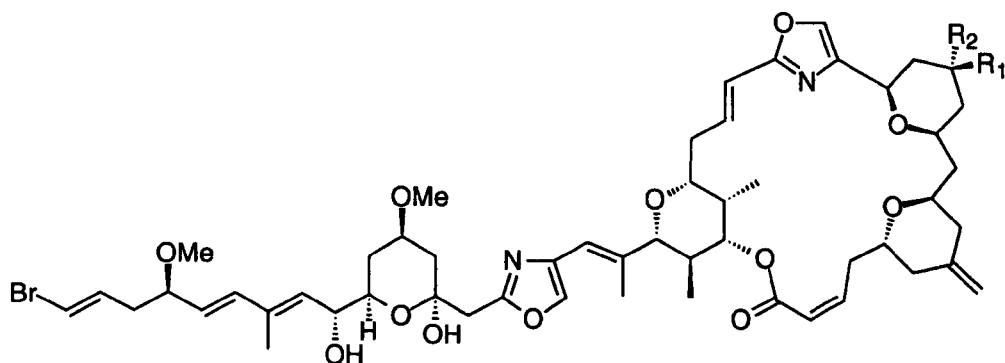


2; R = H Epothilone A

3; R = Me Epothilone B

Throughout this period of activity our own research group has had its interest stimulated by the publication of the structures of a new class of compound; the phorboxazoles,¹⁰ which demonstrate a broad range of biological activity, showing exciting cytotoxic, cytostatic and anti-fungal activity. Phorboxazoles A (4) and B (5)

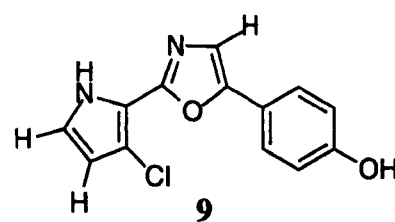
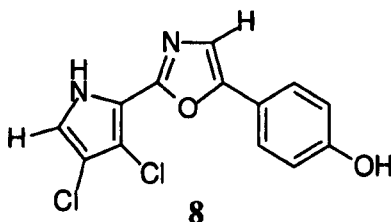
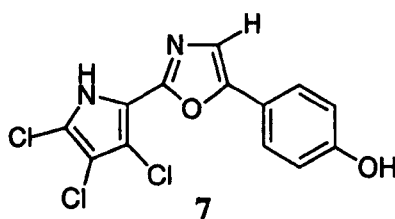
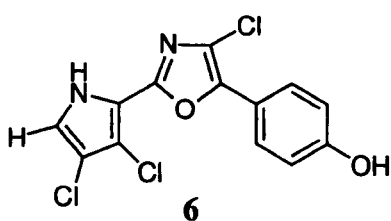
were isolated from the Indian Ocean marine sponge *Phorbas* sp. by Molinski and Searle.^{10a} Their gross structures were first described in August 1995; encompassing an unprecedented molecular architecture of four oxane rings, two oxazole rings, and a 21-membered macrolactone, incorporating fifteen asymmetric centres.



4; $R_1 = H$, $R_2 = OH$ Phorboxazole A

5; $R_1 = OH$, $R_2 = H$ Phorboxazole B

The isolation of the phorboxazoles was only the second report of a natural product from the genus *Phorbas* sp. Four phenylpyrrolyloxazoles named phorbazoles A-D (6-9) were isolated in the early 1990s by Kashman *et al*,¹¹ representing a new class of marine alkaloids containing the chlorinated pyrrole moiety.



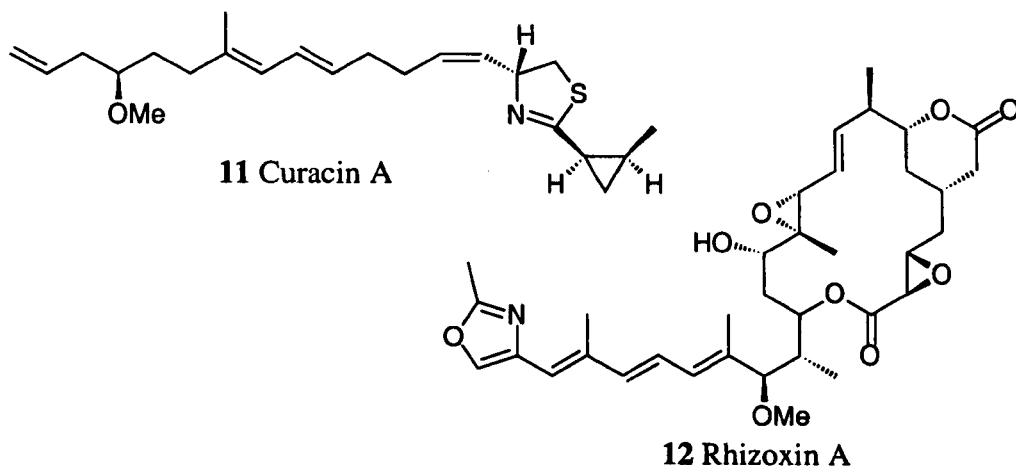
Phorbazoles A-D

Phorboxazoles A (4) and B (5) exhibit *in vitro* anti-fungal activity against *Candida albicans* at 0.1 µg/disc and extraordinary cytostatic activity (mean GI₅₀ < 7.9 x 10⁻¹⁰M in the NCI's 60 tumour cell line); however, most cells were still 100% inhibited at this, the lowest test concentration.^{10a} Phorboxazole B (5) was marginally less active than phorboxazole A (4), yet both show activity of the same order of magnitude as that of spongistatin 1 (10)¹² and are among the most potent cytostatic agents yet discovered.

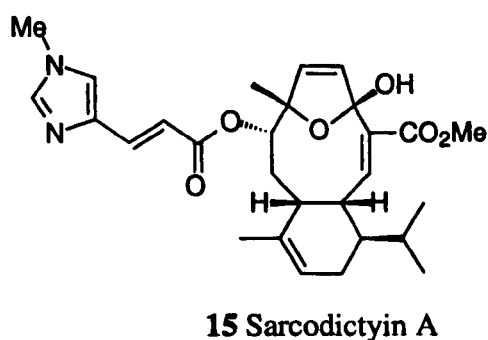
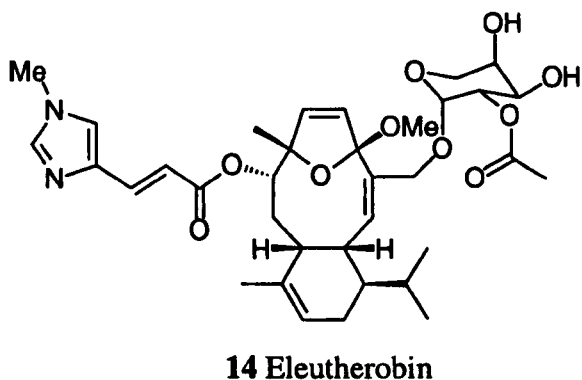
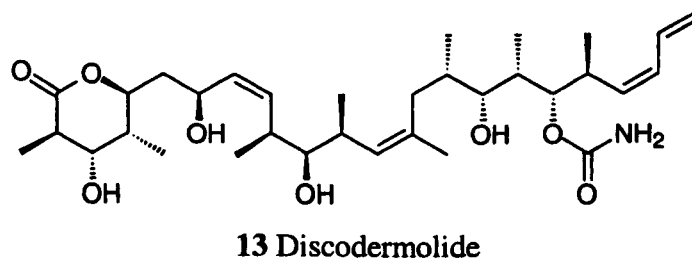
1.2 Biological Mode of Action of Anti-Cancer Drugs

In 1979 Horwitz and co-workers determined the mechanism of action of taxol (1).³ The ability of taxol to arrest carcinogenesis is accounted for by its interaction with the polypeptide tubulin. Tubulin exists in two forms, α- and β-, both of which are composed of approximately 440 amino acids and have molecular weights of around 50kD.¹³ Both forms are structurally similar and together form α-β dimers. The tubulin dimers then assemble in a state of dynamic equilibrium to form large hetero-dimeric bundles called microtubules. Microtubules are the main structural components of the mitotic apparatus and are implicated in a wide array of cellular processes, including cellular movement, cell rigidification and mitosis, the mechanism by which cancerous tumours grow and are spread.

For normal cellular function, there is an absolute requirement that the equilibrium between tubulin, the tubulin dimer and the microtubule is readily reversible. Any change in this delicately balanced equilibrium will dramatically affect cellular properties. Anti-tubulin agents can be classed as two types: *i*, those that cause its disruption and *ii*, those that enhance microtubule polymerisation. The former are exemplified by the natural products curacin A (11)¹⁴ and rhizoxin A (12),¹⁵ which disrupt the cell cytoskeleton by inducing depolymerisation of microtubules to their constituent sub-units α- and β-tubulin.



The latter are represented by taxol (1) and epothilones A (2) and B (3), whereby these compounds have been shown to induce polymerisation of the microtubuli to afford extremely stable and non-functional microtubules which cannot undergo cell division and hence cause cell death.³ Other natural products, also with striking potency, which have been shown to possess the same mechanism of action are the polyketide discodermolide (13),¹⁶ the recently discovered eleutherobin (14),¹⁷ and sarcodictyin A (15).¹⁸



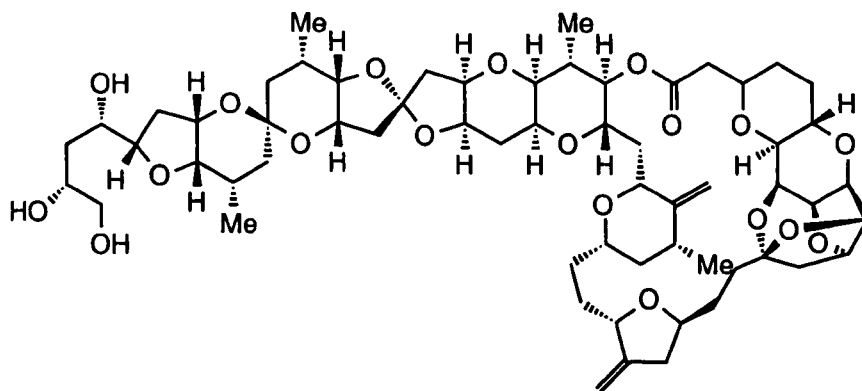
Hence, within a small sub-section of the cell cycle, one can see that there is already complimentary areas for the inhibition of mitosis. However, unlike the anti-tumour agents already discussed, phorboxazole A (4) neither inhibits tubulin polymerisation, nor interferes with the integrity of microtubules. Instead it appears to arrest the cell cycle at the S-phase, that being DNA synthesis and thus provides a complimentary mode of action to the many anti-mitotic natural products already known.^{10c} At this time the precise mode of action of the phorboxazoles is unknown.

1.3 Related Natural Products

With the advent of modern analytical techniques and methods, a number of highly complex and structurally diverse natural products have been isolated and their structures determined. Not only are these some of the most potent compounds known but their fascinating molecular architecture has provided an immense challenge for synthetic chemists in pursuit of total synthesis, allowing for extensive methodology to be developed *en route*.

1.3.1 Oxane Containing Natural Products

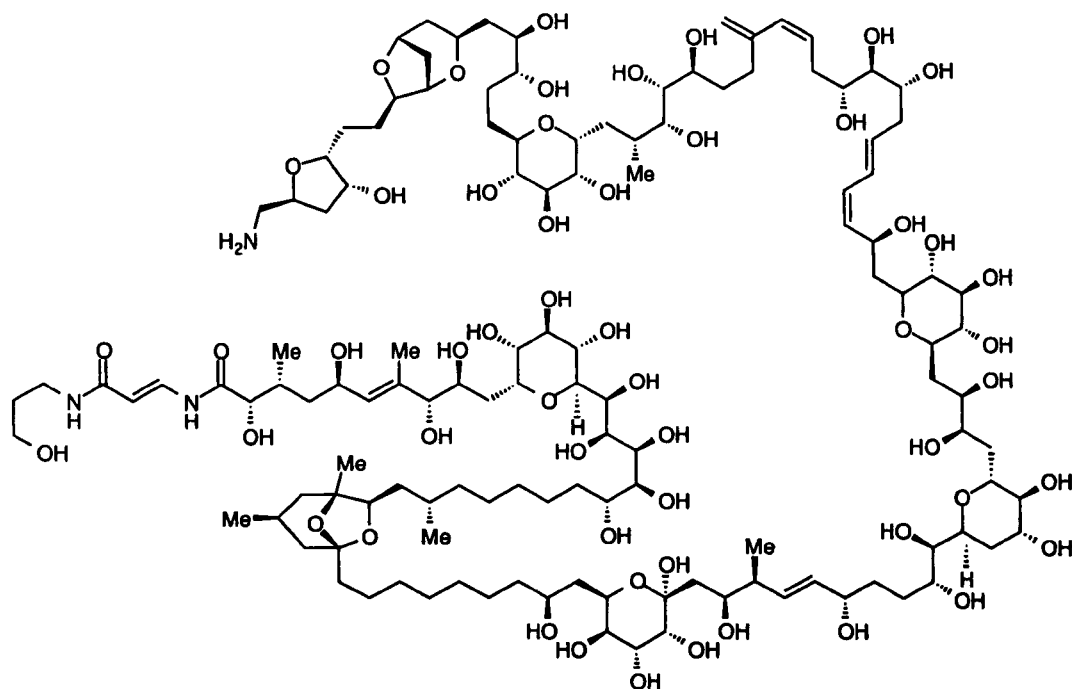
The halichondrins are a class of polyether macrolides isolated originally from the marine sponge *Halichondria okadai* Kadota.¹⁹ Halichondrin B (16) is a tubulin interactive anti-mitotic agent that exhibits extraordinary *in vitro* and *in vivo* anti-tumour activity.¹⁹ Their limited supply and challenging structure, including 32 stereogenic centres, prompted Kishi *et al*, amongst others, to attempt the total synthesis of halichondrin B and this remarkable goal was realised in 1991.²⁰ Kishi used the Ni(II)/Cr(II)-mediated coupling reaction of vinyl iodides with aldehydes extensively to achieve this target and demonstrate the potential of this reaction within natural product synthesis.



16 Halichondrin B

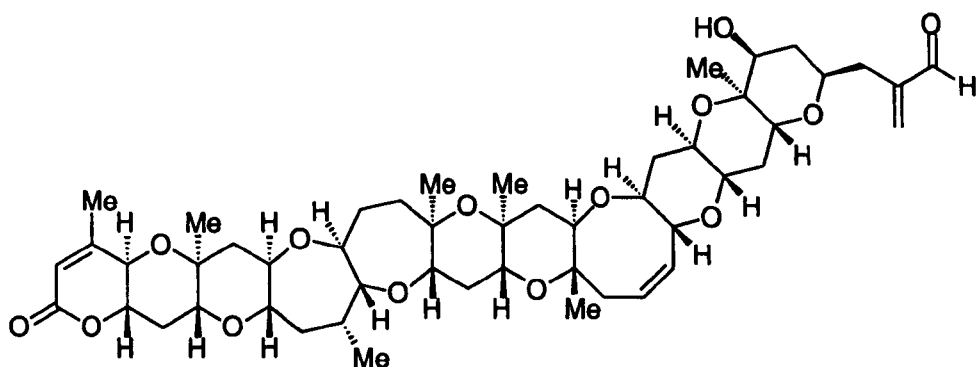
During this time, Kishi's research group was also endeavouring to complete the total synthesis of palytoxin (17). Palytoxin (17) was isolated from the marine soft corals of the genus *Palythoa* and its vast structure was elucidated in 1981.²¹ Until recently, it was claimed to be the most poisonous non-peptidic substance known to man. At the outset of this work, palytoxin was uniquely distinct from molecules with which organic chemists had previously dealt in terms of its size and structural complexity. Palytoxin (17) possesses 71 stereochemical elements and these were defined by a combination of degradation, synthetic and spectroscopic techniques allowing its absolute configuration to be fully determined. Kishi's research group completed this monumental task in 1994, in the process making extensive contributions towards the Ni(II)/Cr(II)-mediated coupling reaction, Suzuki's palladium catalysed diene synthesis and the synthesis of *N*-acyl vinylogous ureas.²² This synthesis is one of the scientific milestones in modern organic chemistry in terms of both the planning, execution and completion of the total synthesis of such a formidable target.

Brevetoxin B (18) is a potent, lipid soluble neurotoxin which is secreted by the algae *Gymnodinium breve* Davis.²³ Brevetoxin B (18) is responsible for the 'red tide' catastrophes, resulting in both mass mortality of marine creatures and human poisoning.²⁴ The imposing structure of brevetoxin B (18) is built up of only carbon,



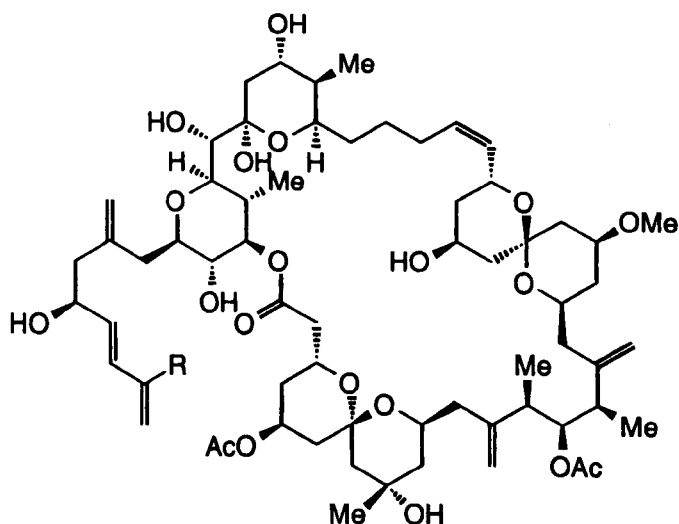
17 Palytoxin

oxygen and hydrogen and distinguished by 11 *trans*-fused ring ethers, containing 23 stereocentres. Nicolaou *et al* described the total synthesis of brevetoxin B (**18**) in 1995, having developed a vast array of new technologies for the synthesis of medium ring ethers in a stereocontrolled manner.²⁵ The completion of brevetoxin B (**18**) unfolded over a period of 12 years and consisted of 123 steps, with the longest linear sequence of 83 steps, with a very impressive average yield of 91%.



18 Brevetoxin B

The spongipyran macrolides are a new class of marine natural products, possessing many structural features in common with the phorboxazoles, including oxane, hemiketal oxane, macrolide and diene moieties. In 1993, three research groups independently reported the isolation and structural elucidation of these spongipyrans derived from the marine sponges *Spongia* and *Spirastrella* (spongistatins),¹² *Cinachyra* (cinachyrolide)²⁶ and *Hyrtios* (altohyrtins).²⁷ The spongipyrans appear to be the most potent inhibitors of cell growth to date, with GI₅₀ values of 2.5-3.5 x 10⁻¹¹M. Further investigations revealed that spongistatin 1 (**10**) inhibits mitosis by binding to tubulin and blocking microtubule assembly.^{12d} Since only the altohyrtins structure elucidation provided an absolute configuration assignment, it was these that were targeted initially for synthesis. Very recently (Dec. 1997) Evans *et al* reported the completion of a synthesis of altohyrtin C (**19**) showing it to be identical to spongistatin 2 (**19**).²⁸ Closely following this was Kishi's disclosure of the first synthesis of altohyrtin A (**10**) showing that it was identical to spongistatin 1 (**10**).²⁹ Both these syntheses used a plethora of modern chemistry for the assembly of these structurally complex substrates and thus provided an alternative source of these scarce and highly potent anti-cancer agents.



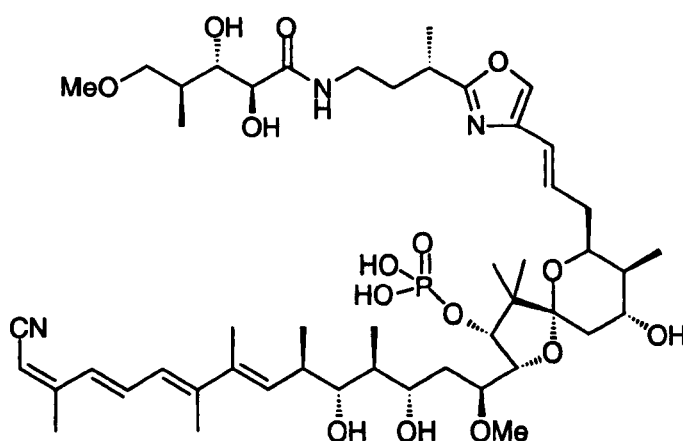
10; R = Cl Altohyrtin A, Spongistatin 1

19; R = H Altohyrtin C, Spongistatin 2

1.3.2 Oxazole Containing Natural Products

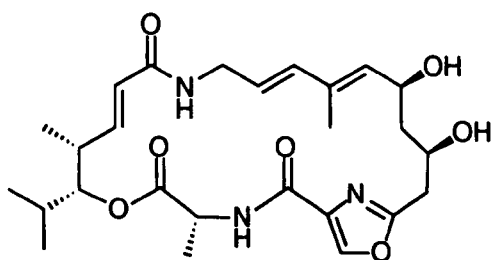
The occurrence of oxazoles in marine natural products has recently become quite common. Most of these secondary metabolites contain isolated oxazole rings, but recent interest has become focused on natural products which contain two or three contiguously linked oxazoles. This section of the thesis is not intended to be a thorough treatise of oxazole containing compounds but rather just to highlight some of the many oxazoles in Nature that have been of interest within our research group and that of others.

Calyculin A (**20**) was isolated from the marine sponge *Discodermi calyx* in 1986.³⁰ Its structure was elucidated by X-ray crystallography showing the presence of a 2,4-disubstituted oxazole amongst a wide array of other functionality. Calyculin A (**20**) has also aroused considerable interest due to its striking biological activity exemplified by the inactivation of the serine / threonine protein phosphatases 1 and 2A.³¹ The total synthesis of calyculin A (**20**) has been reported by the research groups of Evans *et al* in 1992,³² and Masamune *et al* in 1994,³³ with a formal synthesis also described by Shioiri *et al* in 1996.³⁴

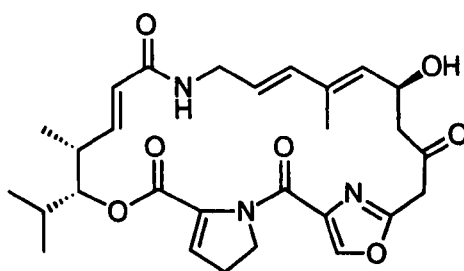


20 Calyculin A

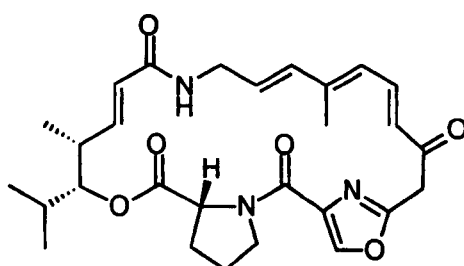
The oxazole unit also occurs in many of the virginiamycin family of antibiotics, produced by several micro-organisms. The group A virginiamycins have a common, 23-membered macrolactone core which accommodates a 2,4-disubstituted oxazole, an acrylamide unit, a polyene segment and an amino acid residue. The broad spectrum antibiotic madumycin II (**21**) was isolated from a culture of *Streptomyces graminofaciens* in 1976³⁵ but it was not until 1996 that a total synthesis of this compound was reported by Meyers *et al.*³⁶ A short time later, the macrocyclic antibiotic virginiamycin M₂ (**22**) was isolated from *Streptomyces virginiae*, which has been recognised as a cholecystokinin antagonist for treating panic, anxiety and cancer withdrawal.³⁷ Schlessinger *et al* reported its total synthesis in 1996.³⁸ The synthesis of the related antibiotic 14,15-anhydropristinamycin II_B (**23**) was accomplished by Pattenden *et al*, again in 1996.³⁹



21 Madumycin II

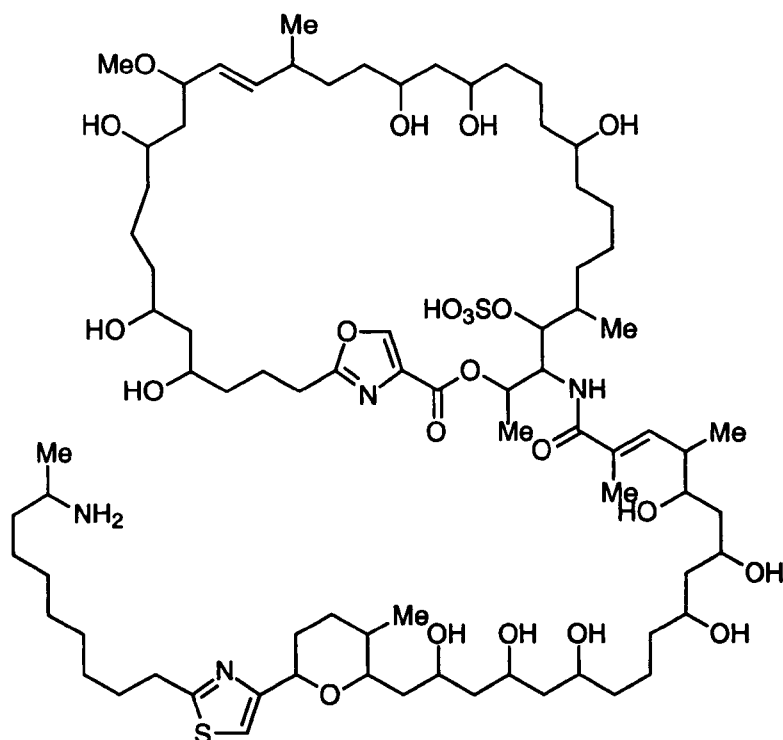


22 Virginiamycin M₂



23 14,15-anhydropristinamycin II_B

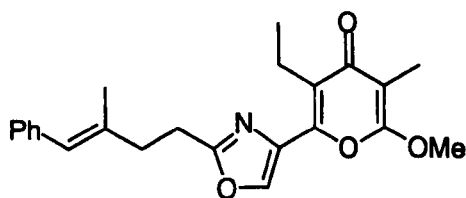
In 1993, the novel macrolide theonezolid A (**24**) was isolated from the Okinawan marine sponge *Theonella* sp.⁴⁰ Theonezolid A (**24**) belongs to a new class of



24 Theonezolid

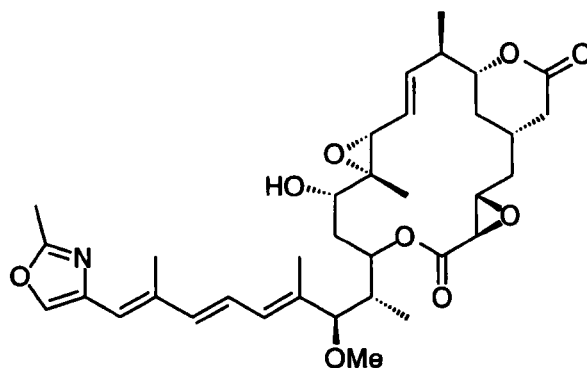
polyketide natural products, with unique structural features, consisting of two principal fatty acid chains, incorporating a 2,4-disubstituted oxazole, a 2,4-disubstituted thiazole and a tetrahydropyran. Theonezolid A (**24**) exhibits cytotoxicity against the murine lymphoma L1210 and human epidemoid carcinoma KB cells *in vitro*.⁴⁰

Phenoxan (**25**) was recently isolated from a soil micro-organism and found to exhibit anti-HIV activity.⁴¹ Its structure is characterised by the presence of a 2,4-disubstituted oxazole bearing a pyran-4-one at the 4-position of the oxazole, analogous to the oxazole-pyran moiety in the phorboxazoles. To date there have been two published syntheses of phenoxan (**25**).⁴²



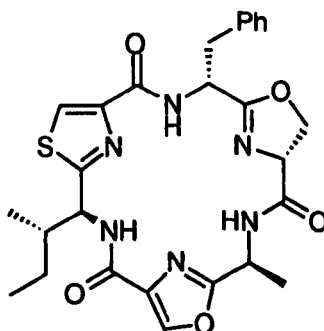
25 Phenoxan

Rhizoxin A (**26**) is a highly functionalised macrolactone from the pathogenic fungus *Rhizopus chinesis*.^{15a} It differs from many of the natural products discussed in this section, by the presence of the oxazole at the terminus of the side chain. Rhizoxin A (**26**) has stimulated much interest within the chemical community,⁴³ not only by its intriguing structure, but also by exhibiting diverse and significant biological activity.



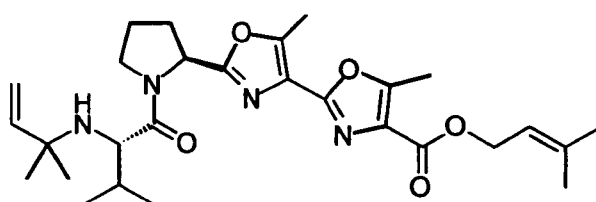
26 Rhizoxin A

The presence of oxazoles within cyclic peptide natural products has been well documented.⁴⁴ The high density of hetero-atoms within the central cavity of the macrolide has raised questions about their biosynthesis and *in vivo* function.⁴⁵ The hexapeptide raocyclamide A (**27**) was isolated from the cyanobacterium *Oscillatoria raoi*, and incorporates an oxazole, oxazoline and thiazole units.⁴⁶ The total synthesis of raocyclamide A (**27**) has recently been described by Freeman and Pattenden.⁴⁷



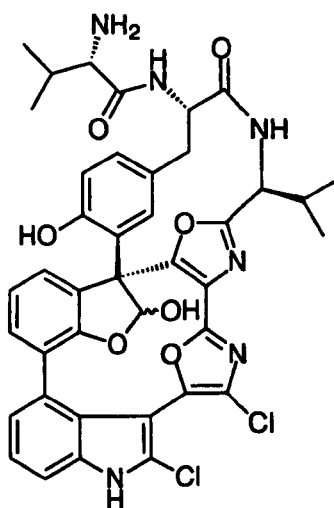
27 Raocyclamide A

Natural products containing two or three contiguous oxazole units are significantly less common. Muscoride A (**28**), is a novel *bis*-oxazole based peptidic alkaloid isolated from the terrestrial cyanobacterium *Nostoc muscorum*, which displays weak antibacterial activity.⁴⁸ The molecule is unique because the *bis*-oxazole unit is derived presumably from two threonine residues making it the only natural product bearing two contiguous 5-methyl oxazoles. The total synthesis of muscoride A (**28**) has been accomplished recently by two groups, Wipf *et al* in 1996,⁴⁹ and Pattenden *et al* in 1997.⁵⁰



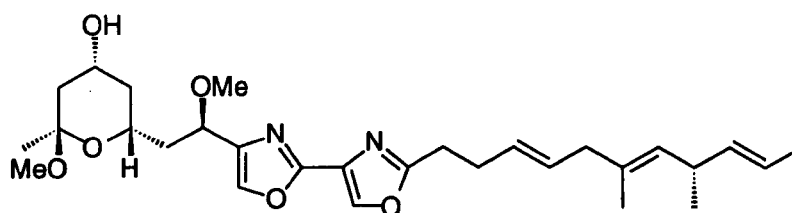
28 Muscoride A

The *bis*-oxazole containing compound diazonamide A (**29**), isolated from the colonial ascidian *Diazona chinesis* is composed of a highly complex bicyclic framework encompassing a chlorinated indole, a benzofuran and a chlorinated *bis*-oxazole moiety.⁵¹ Dizonamide A (**29**) displays potent *in vitro* cytotoxicity, yet its structural complexity has eluded the organic chemist and a total synthesis has not been reported.



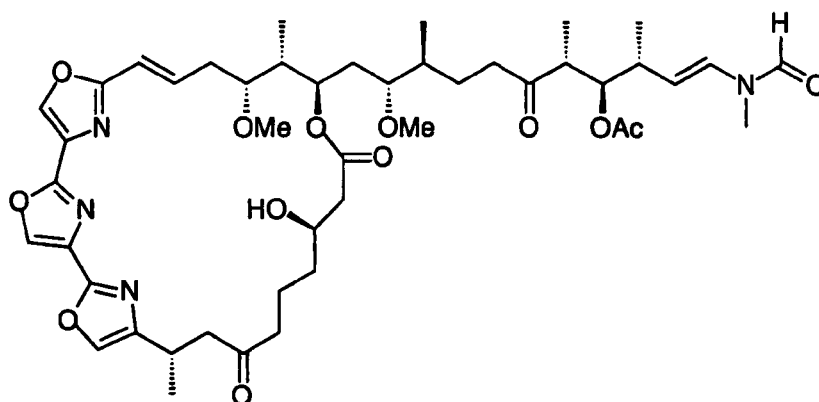
29 Dizonamide A

A further *bis*-oxazole containing compound, hennoxazole A (**30**) was isolated from the marine sponge *Polyfibrospongia* sp. and was shown to be highly active against the herpes simplex virus.⁵² Its structure is characterised by the presence of a 2,4-disubstituted *bis*-oxazole moiety, a pyranoid glycoside and a rather unusual skipped triene unit. Wipf *et al* reported the total synthesis of the enantiomer of hennoxazole A in 1995, thus confirming the previous structure elucidation.⁵³



30 Hennoxazole A

Ulapualide A (**31**) is a member of a novel family of oxazole containing macrolides, first isolated from the egg masses of the nudibranch *Hexabranhus sanguineus*.⁵⁴ It belongs to an emerging class of secondary metabolites including halichondramides,⁵⁵ kabiramides,⁵⁶ and mycalolides,⁵⁷ all of which contain a contiguous *tris*-oxazole unit as the rigid backbone of a macrolactone core, only differing in oxidation patterns and methyl substitution. Ulapualide A (**31**) shows a variety of interesting biological activity including anti-leukaemic, anti-fungal and ichthyotoxic properties. Although the stereochemical integrity of ulapualide A is in some doubt, Chattopadhyay and Pattenden have recently completed a total synthesis of the entire ulapualide framework.⁵⁸

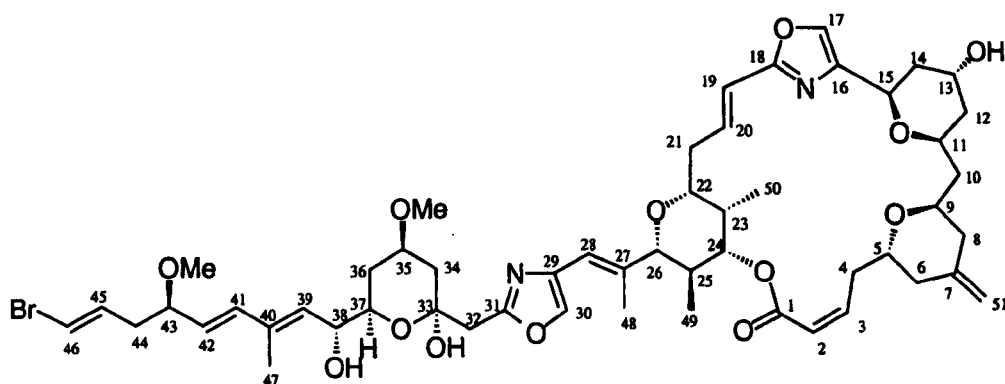


31 Ulapualide A

1.4 Isolation and Structure Elucidation of the Phorboxazoles

Molinski *et al* isolated the phorboxazoles from an extract of the Indian Ocean marine sponge *Phorbas* sp. and disclosed their structure in August 1995.^{10a} The methanol extract of the sponge (236g dry weight) was subjected to solvent partitioning and extensive chromatography to give phorboxazole A (**4**; 95.1mg, 0.040%) and phorboxazole B (**5**; 40.5mg, 0.017%), both as pale yellow amorphous solids. Both compounds were shown to be potent cytostatic agents which prompted Molinski to determine their full structure.

The molecular formula of both (**4**) and (**5**) was established as $C_{53}H_{71}N_2O_{13}Br$ by high resolution mass spectrometry. Extensive 1D and 2D NMR analysis gave rise to five substructures which on further examination of the data could be pieced together to give the gross structure of the phorboxazoles, showing the presence of two oxazoles, four pyran rings and a twenty one membered macrolide. The relative stereochemistry of the side chain hemiketal ring and the macrolide were then determined by analysis of 1H - 1H coupling constants and ROESY data, but these could not be correlated together at this time. By comparison of the nmr spectra for (**4**) and (**5**), they showed only a very small difference in one of the substructures, Molinski suggested that phorboxazole B (**5**) was the C-13 epimer of phorboxazole A (**4**).^{10a}



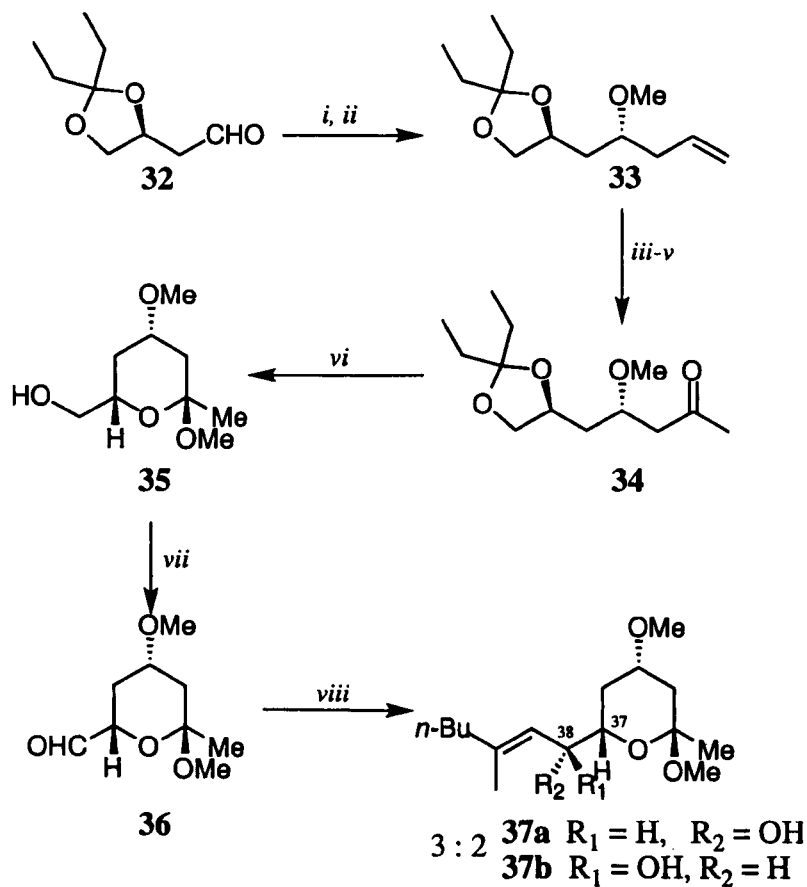
4 Phorboxazole A

The next task was to determine the configuration of the remaining five stereogenic centres of the side chain and the absolute stereochemistry of the phorboxazoles. Molinski was unable to obtain satisfactory samples for X-ray analysis and thus proceeded to use chemical and spectroscopic methods. By application of Kakisawa's modification of the Mosher's ester method,⁵⁹ the absolute stereochemistries of the C-13 and C-38 stereocentres (phorboxazole numbering) were determined, and hence the absolute stereochemistry of the macrolide.^{10b}

From the now known C-38 alcohol configuration the stereochemistry of the hemiketal ring was determined by spectroscopic comparison with a synthetic model and examination of the H-37 and H-38 vicinal coupling constant. Thus, both *erythro* (**37a**) and *threo* (**37b**) model allylic alcohols were synthesised as detailed in Scheme 1.^{10b}

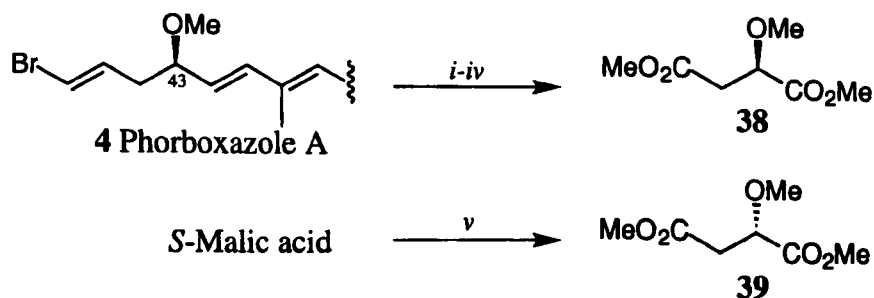
The *threo* isomer (**37b**) possessed a H-37 to H-38 coupling constant of 8.0Hz which matched that of phorboxazole A (**4**) ($J = 7.9\text{Hz}$), proving the *threo* configuration exhibited in phorboxazole A. Using this in association with the relative stereochemistry of the hemiketal ring, as determined previously, allowed fourteen of the fifteen stereogenic centres to be determined.

It only remained at this time for the determination of the stereochemistry of the remaining C-43 stereocentre. Due to the remoteness of this centre, this proved to be a difficult task but Molinski was able to solve this problem by degradation of the natural product.^{10c} Thus, ozonolysis of phorboxazole A (**4**), followed by oxidation of the resulting mixed ozonides with performic acid and subsequent treatment of the residue with diazomethane gave a mixture of methyl esters. Separation of this mixture by silica gel chromatography gave a non-polar fraction containing **38**, determined to be dimethyl methoxy succinate (**38**). Co-elution of the degraded product with synthetic samples of (*S*)-dimethyl methoxy succinate (**39**) and racemic dimethyl methoxy succinate, showed that the C-43 stereocentre of phorboxazole A had the *R* configuration (**Scheme 2**).^{10c}



Reagents: *i*, $\text{Bu}_3\text{SnCH}_2\text{CHCH}_2$, $\text{Ti}(\text{OiPr})_4$, (*R*)-BINOL (cat.), 76%; *ii*, NaH, MeI, 95%; *iii*, OsO_4 , NMO, NaIO_4 , 95%; *iv*, MeLi, 84%; *v*, Swern Ox., 87%; *vi*, CSA, MeOH, 95%; *vii*, Swern Ox., 84%; *viii*, $n\text{-BuC}\equiv\text{CH}$, Me_3Al , Cp_2ZrCl_2 , 70%.

Scheme 1



Reagents: *i*, O_3 , MeOH; *ii*, HCO_2H , H_2O_2 ; *iii*, CH_2N_2 , MeOH, Et_2O ; *iv*, silica chromatography (Et_2O elution); *v*, MeI, Ag_2O , Et_2O , 65%.

Scheme 2

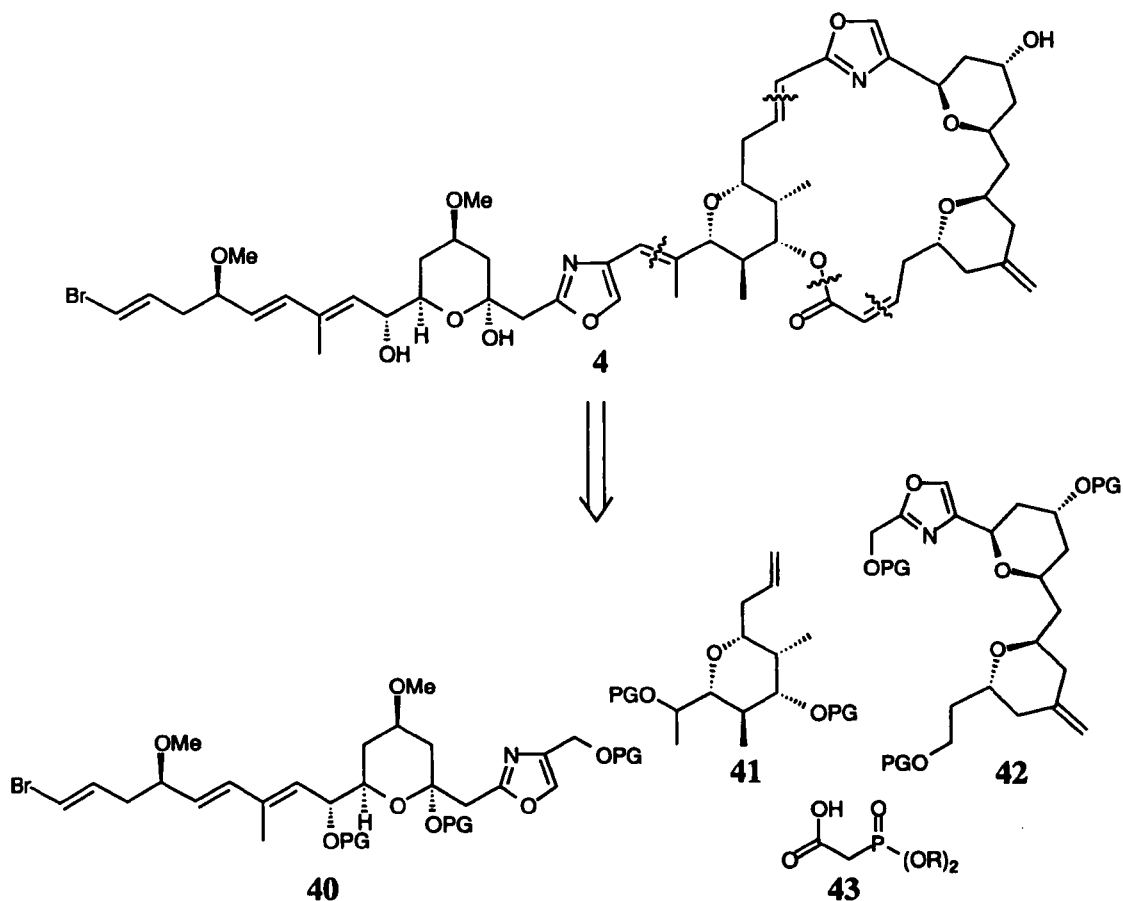
Thus, the complete configuration of phorboxazole A (**4**) was determined as *5S*, *9R*, *11S*, *13R*, *15R*, *22R*, *23S*, *24S*, *25R*, *26R*, *33S*, *35R*, *37R*, *38R*, *43R*. With the task of elucidating the full structure of the phorboxazoles complete, we were now in a position to proceed towards a total synthesis of the phorboxazoles with the correct choice of chiral pool starting materials.

1.5 Retrosynthetic Analysis

With the unprecedented structure of the phorboxazoles now known, we set ourselves the task of devising a retrosynthetic analysis to provide the key target fragments for assembly in an efficient and convergent manner. Our choice of disconnections was based on the flexibility we wished to employ when we arrived at the assembly stage. Thus, disconnection across the three olefin units and the lactone unit gave us many viable options for both the type of coupling to be used and the order. This gave rise to three key fragments, the side chain (**40**), the central pyran (**41**) and the oxazole *bis*-pyran (**42**), each containing five stereogenic centres and a variety of functionality (Scheme 3).

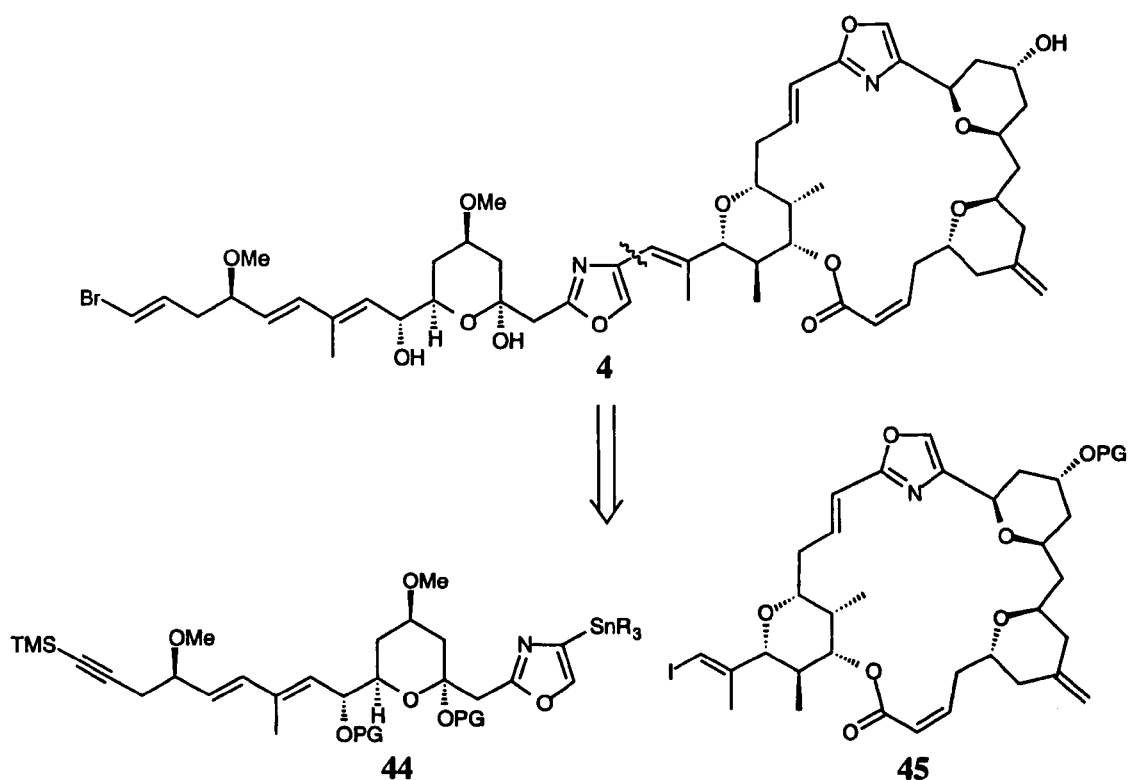
We envisaged assembly of these fragments by a combination of methods including the Wittig reaction, Wadsworth-Emmons reaction, Julia reaction and esterification. It was our initial thought to make use of Still's modification of the Wittig reaction⁶⁰ to form the (*Z*)-olefin as the macrocyclisation step.

We thank Professor Molinski for providing preprints of the subsequent communications detailing the side chains chirality and the absolute configuration of the phorboxazoles.^{10b,c}



Scheme 3

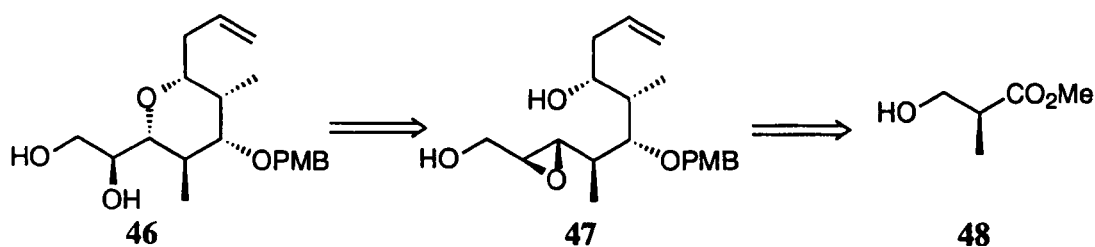
An alternative method of assembly of the key fragments is by amide bond formation, prior to oxazole formation. Many of the compounds *en route* to these fragments have the functionality for an amine or a carboxylic acid terminus, which would be necessary to make use of this route. One further strategy would be to make use of the Stille reaction for coupling appropriately functionalised vinyl halides with oxazole stannanes or *vice versa*. This approach would be particularly attractive in view of the Pattenden group interest in the application of the Stille reaction to natural product synthesis (Scheme 4).^{39,61}



Scheme 4

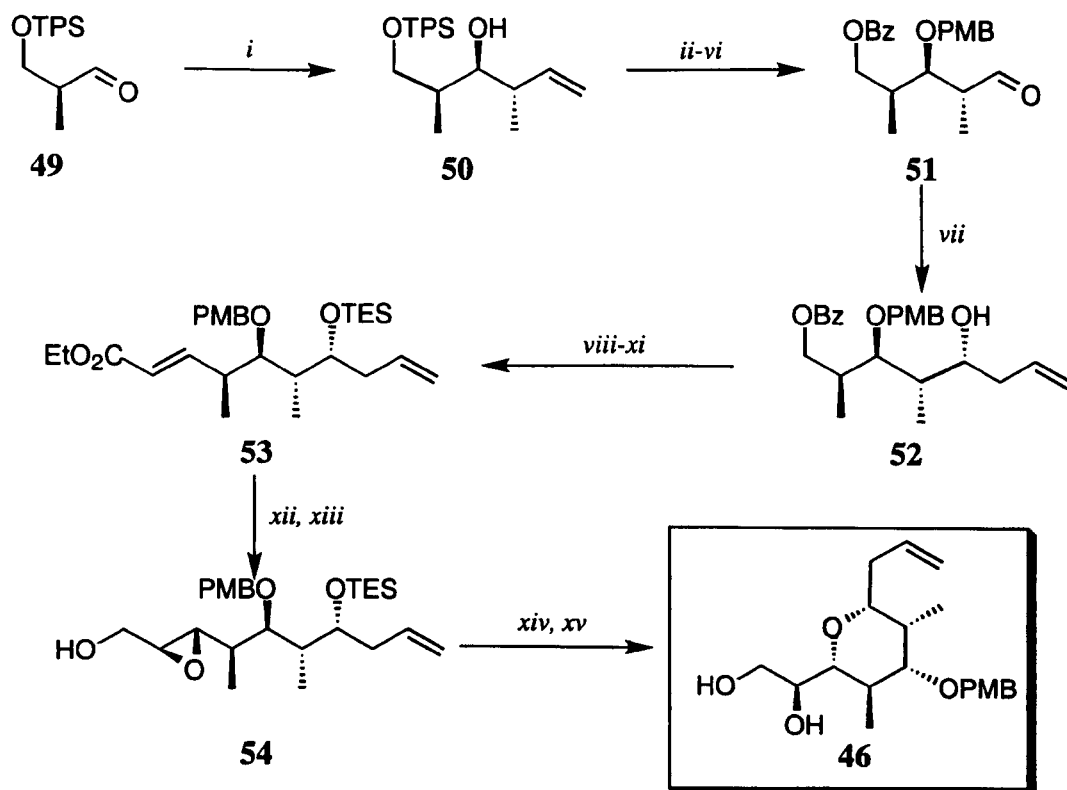
1.6 Synthetic Work Towards the Central Pyran Core

Detailed in this thesis are the author's synthetic studies towards two of the key fragments of the phorboxazoles, namely the oxazole *bis*-pyran (**42**) and the side chain (**40**). One of my colleagues Dr Tao Ye simultaneously executed a synthesis of the central pyran core (**41**) using a strategy based on the Lewis acid mediated ring closure of a hydroxyl group onto an epoxide, ultimately derived from the chiral pool material (*S*)-3-hydroxy-2-methyl propionate (**48**) (Scheme 5).⁶²



Scheme 5

Thus, (*S*)-3-hydroxy-2-methyl propionate (**48**) was converted into the corresponding aldehyde (**49**), which was next subjected to crotylboration conditions to give the secondary alcohol (**50**) in 76% yield and with excellent diastereoselectivity (92% de). Functional group manipulations then gave rise to the aldehyde (**51**), which was next allylated under substrate control with allyltributyltin and under Lewis acid catalysis to give the homoallylic alcohol (**52**) in 94% yield and with >95% diastereoselectivity. Transformations next gave rise to the allylic alcohol which was then treated under Sharpless epoxidation conditions to give the corresponding epoxide (**54**) in 94% yield. Treatment of **54** with TBAF gave the alcohol (**47**) which upon treatment with titanium tetra-*i*-isopropoxide in refluxing benzene gave the 2,6-*cis*-tetrahydropyran (**46**) in 76% yield (**Scheme 6**).⁶² The stereochemical outcome of the ring closure was determined by extensive 1D and 2D NMR analysis.



Reagents: *i*, a) (-)- β -(*E*)-crotyl-(*ip*c)₂B; b) Et₃N, H₂O₂, 76%; *ii*, PMBOC(NH)CCl₃, TfOH, Et₂O; *iii*, TBAF, THF; *iv*, PhCOCl, DMAP (cat.), Py., 49% (3 steps); *v*, OsO₄, NMO; *vi*, NaIO₄, THF, H₂O, 87% (2 steps); *vii*, SnBu₃Allyl, BF₃·Et₂O, 94%; *viii*, TES-OTf, 2,6-lutidine; *ix*, DIBAL-H, hexane, 82% (2 steps); *x*, Swern ox.; *xi*, (EtO)₂P(O)CH₂CO₂Et, NaHMDS, 63% (2 steps); *xii*, DIBAL-H, hexane, 89%; *xiii*, (+)-DET, Ti(O*i*Pr)₄, TBHP, 95%; *xiv*, TBAF, THF, 94%; *xv*, Ti(O*i*Pr)₄, C₆H₆, Δ , 76%.

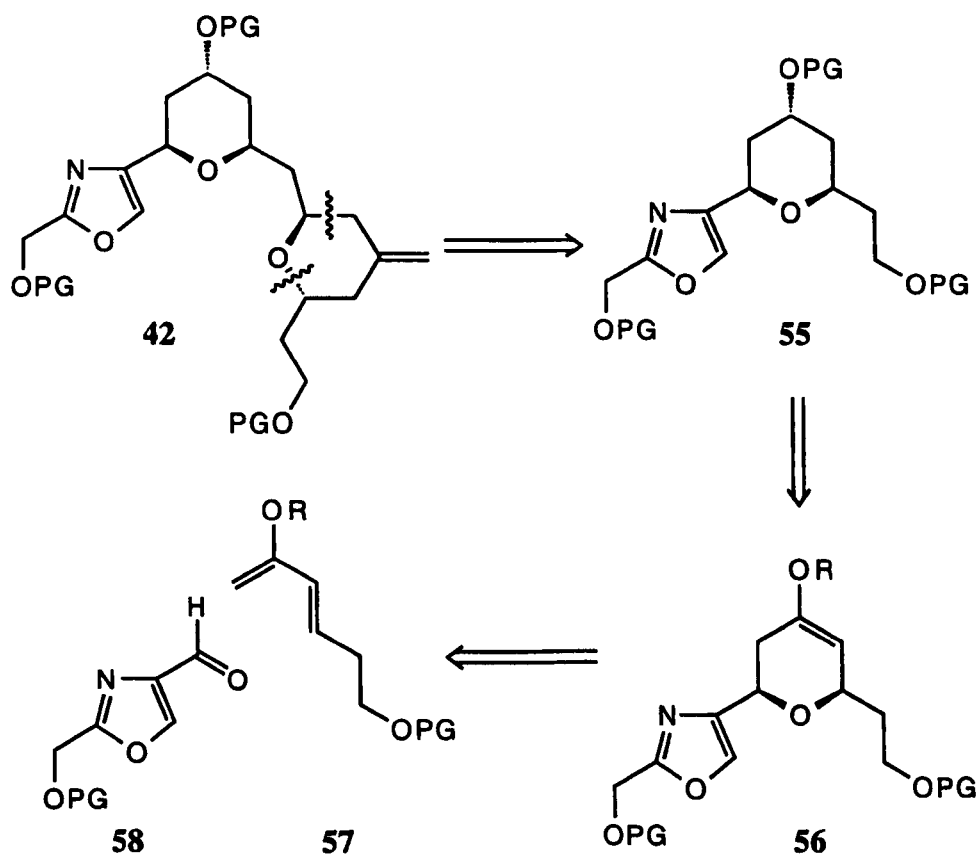
Scheme 6

2. RESULTS AND DISCUSSION

2.1 Synthetic Studies Towards the Oxazole *bis*-Pyran Unit

2.1.1 Retrosynthetic Analysis

At the outset of this period of research, only the relative stereochemistry of the macrolide portion of the phorboxazoles had been determined.^{10a} For this reason we directed our initial efforts towards this fragment. We believed that upon the development of the necessary methodology, we would be able to apply it to the correct enantiomer, once the absolute stereochemistry had been determined. As previously discussed, we devised a retrosynthetic strategy making use of the extensive array of functionality present. Thus, the macrolide was disconnected to the central pyran (**41**) and the oxazole *bis*-pyran unit (**42**) (Scheme 3). Further disconnection of the oxazole *bis*-pyran (**42**) across the *trans*-pyran gave rise to our initial target, the oxazole *cis*-pyran (**55**), incorporating three stereogenic centres (Scheme 7).



Scheme 7

We envisaged the possibility of utilising the hetero Diels-Alder reaction as a highly regio- and stereoselective method for the construction of the tetrahydropyran moiety in **55**. Furthermore, this approach allows for the introduction of the requisite functionality for installation of all three stereocentres in a very short sequence of steps.

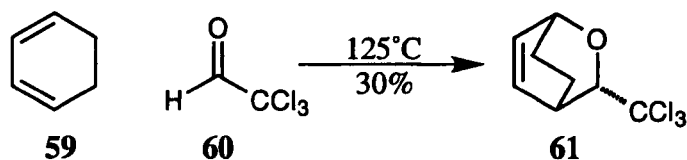
2.1.2 The Hetero Diels-Alder Reaction

The Diels-Alder reaction⁶³ is one of the most powerful carbon-carbon bond forming reactions in organic chemistry, allowing the creation of two new bonds and up to four new stereocentres simultaneously, usually in a highly regio- and stereoselective manner. The Diels-Alder hetero atom counterpart has received much less attention until recently, where it has been recognised as a useful tool in the synthesis of heterocycles, with a wide variety of hetero atom containing dienes and dienophiles being employed. Several comprehensive reviews have been written on this subject and the reader is referred to these for a more thorough treatise on all aspects of the hetero Diels-Alder reaction.⁶⁴

This section of the thesis is intended to be a brief review on the hetero Diels-Alder reaction applicable to the project and will concentrate solely on carbonyl dienophiles, more specifically aldehydes, and their reactions with oxygenated dienes.

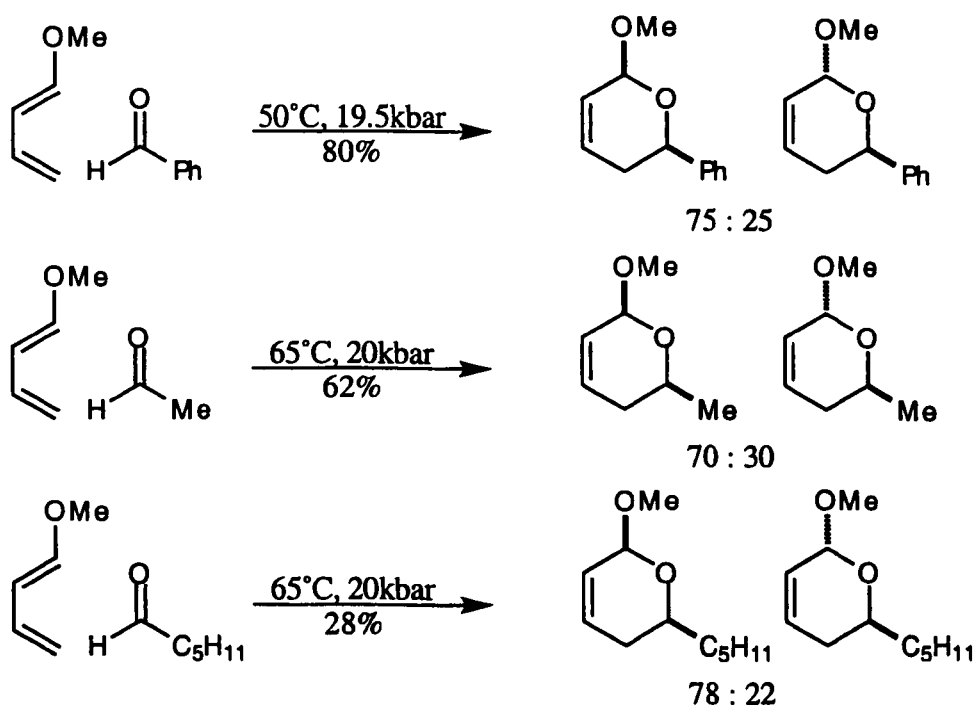
The reaction of a carbonyl compound with a 1,3-diene unit gives rise to a 2,3-dihydropyran derivative. This approach has been used widely in the formation of oxygen containing heterocycles, but is limited by the reactivity of the carbonyl dienophile and diene partners. In general, reactions of this type proceed poorly with aliphatic and aromatic aldehydes, unless highly reactive dienes and/or Lewis acid catalysts are used. Electron deficient aldehydes are generally more reliable dienophiles in both thermal and acid-catalysed cycloadditions with alkyl substituted 1,3-dienes. It has been shown that chloral (**60**), reacts with simple 1,3-dienes to afford reasonable yields of [4+2]

cycloadducts.⁶⁵ The stereochemistry of the Diels-Alder reaction of cyclohexadiene (**59**) and chloral (**60**), under thermal conditions has been investigated and was established unambiguously to give the *endo*-adduct (**61**) (Scheme 8).⁶⁶



Scheme 8

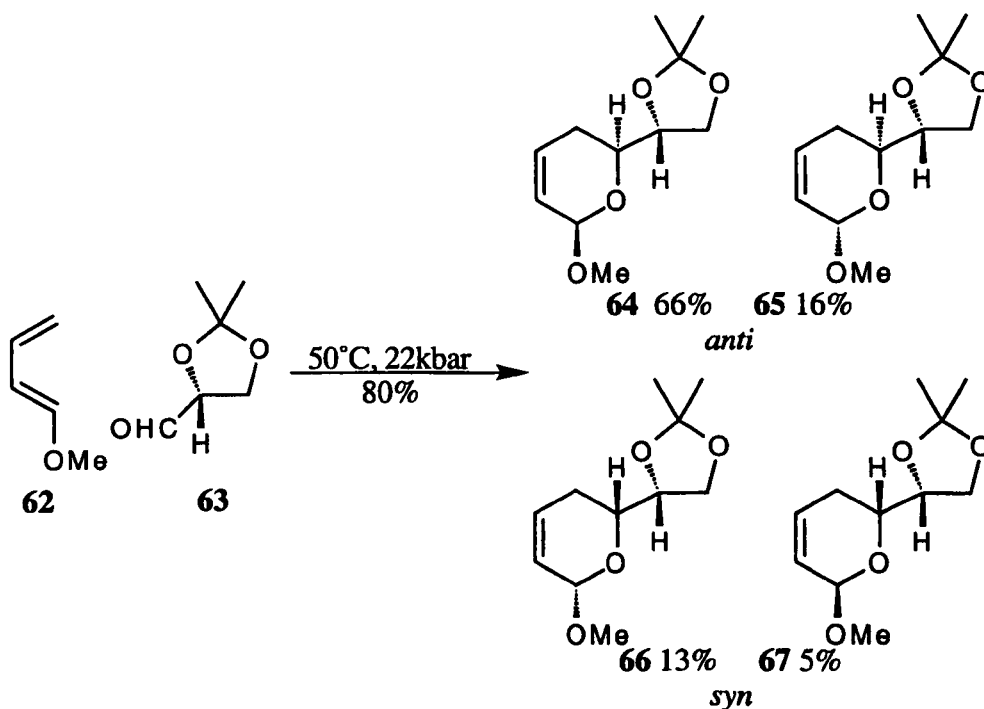
In view of the low reactivity of simple aliphatic and aromatic aldehydes with dienes, Jurczak and co-workers have shown that the scope of carbonyl dienophile cycloadditions may be broadened if reactions are carried out under neutral conditions at high pressure (Scheme 9).⁶⁷



Scheme 9

In an extension of this methodology Jurczak *et al* found that under high pressure *trans*-1-methoxybutadiene (**62**) reacts with (*R*)-glyceraldehyde acetonide (**63**) to give adducts with a high degree of stereoinduction (Scheme 10).⁶⁸ Significantly the

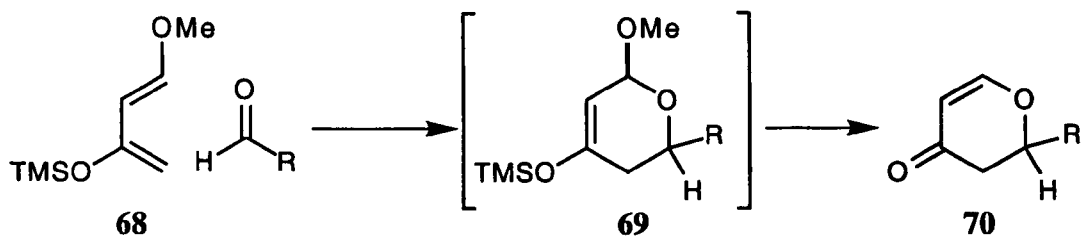
cycloaddition shows a 82:18 facial selectivity with respect to the diene, (*i.e. anti:syn*), which can be rationalised by a “Felkin-like” mode of approach.



Scheme 10

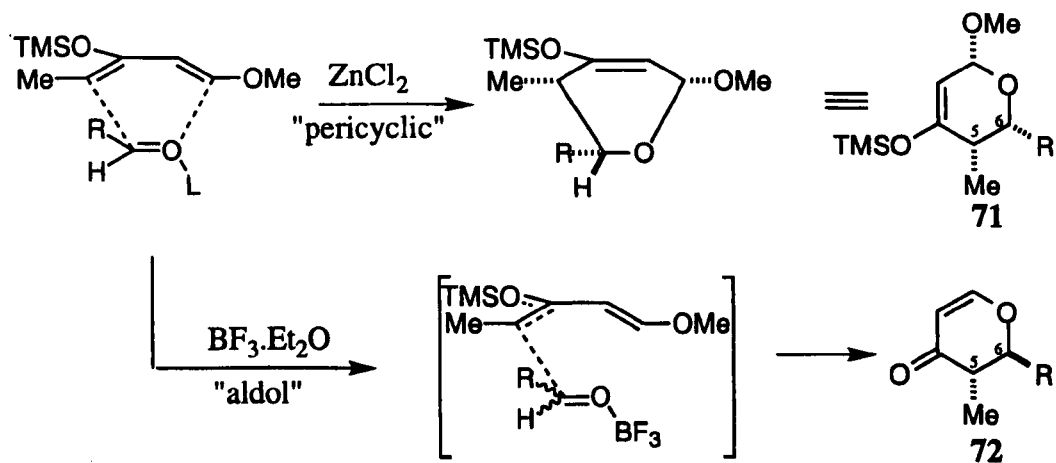
Without any doubt, the most pioneering work in this field was developed by Danishefsky *et al*, by the recognition that simple aldehydes will react readily with many electron rich oxygenated dienes under Lewis acid catalysis. In their initial reports the Danishefsky group described the reactions of the oxygenated diene (**68**), which became known as Danishefsky’s diene, with a wide range of unactivated aldehydes using zinc chloride or boron trifluoride diethyl etherate as a catalyst.⁶⁹ This furnished a 2,3-dihydro- γ -pyrone (**70**), presumably *via* the intermediacy of a transient [4+2] cycloadduct (**69**) (Scheme 11).

The Danishefsky research group has described a series of detailed investigations into the mechanism,⁷⁰ stereochemistry,⁷¹ and the synthetic applications⁷² of this process. Mechanistically the cycloaddition reaction is rather complex. Depending on the catalyst or solvent used and the reaction substrates; pericyclic and/or Mukaiyama aldol-like



Scheme 11

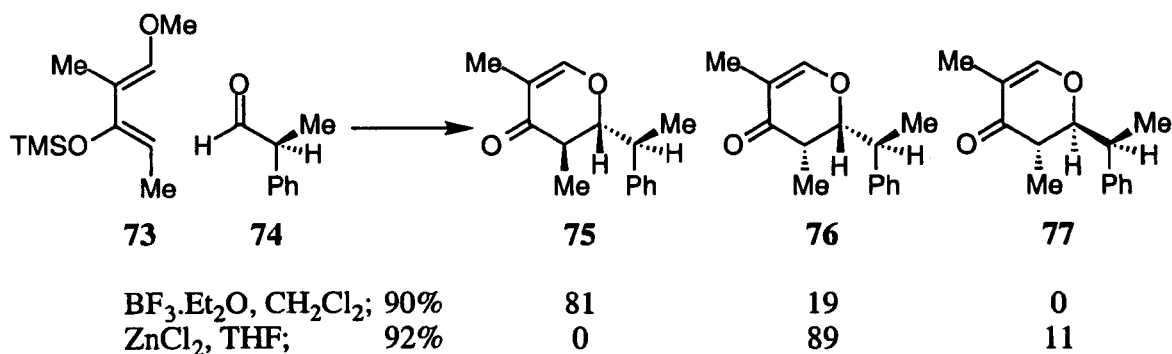
pathways may be involved. With zinc chloride it is assumed that chelation of the aldehyde with the Lewis acid occurs in an *anti* manner, and that the steric bulk of the R-group is less than that of the Lewis acid-solvent complex L. This favours a Diels-Alder transition state with the R-group in an *endo* orientation, resulting in the adducts having *cis* relative stereochemistry at C-5,6 (71) (Scheme 12). Furthermore, this selectivity could be reversed to give a C-5,6 *trans* arrangement (72) by employing boron trifluoride diethyl etherate as the catalyst, which doesn't exhibit such a steric preference for an *endo* approach. It was postulated that reactions catalysed by boron trifluoride diethyl etherate were not concerted, but probably involved an aldol-like pathway (Scheme 12).⁷⁰



Scheme 12

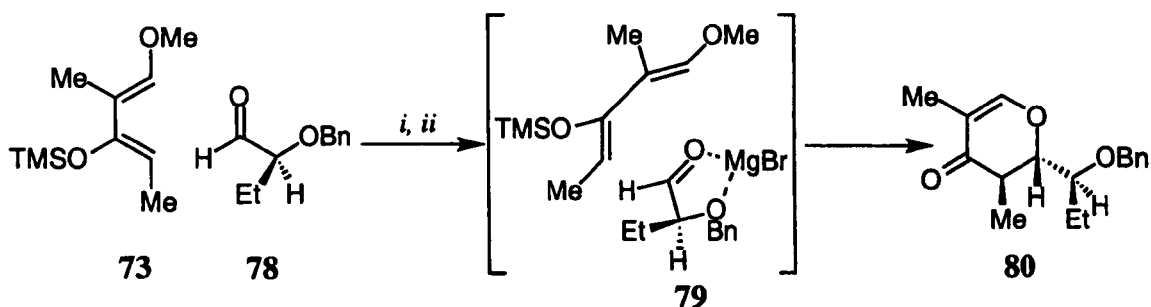
High levels of stereochemical induction can also be achieved by the use of an α -substituted chiral aldehyde.⁷¹ These cycloadditions show excellent facial selectivity depending on the nature of the α -substituent used and the Lewis acid employed.

Scheme 13 shows the facial control obtained with α -methylphenylacetaldehyde (**74**) and a highly oxygenated diene (**73**) using two different catalysts.^{71a,b} In both cases the facial selectivity was the same (*i.e.* Cram), but as shown previously the C-5,6 stereochemistry was reversed using boron trifluoride diethyl etherate as the catalyst.



Scheme 13

Good facial selectivity was also found in the case of α -alkoxyaldehydes (*cf.* **78**), but again this was highly dependant on the Lewis acid and substrates used. With magnesium bromide as catalyst cycloaddition was shown to occur *via* a chelated aldehyde (**79**) with the diene (**73**) attacking from the least congested face. For steric reasons an *exo* transition state in a pericyclic process is favoured in this case, giving rise to a single diastereomer of the dihydropyran (**80**) (Scheme 14).^{71c}

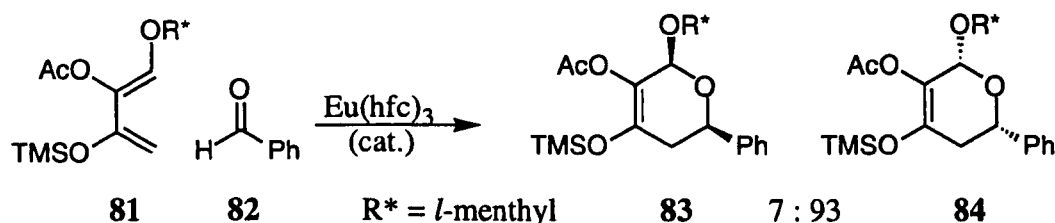


Reagents: *i*, MgBr_2 , THF; *ii*, AcOH, 68%.

Scheme 14

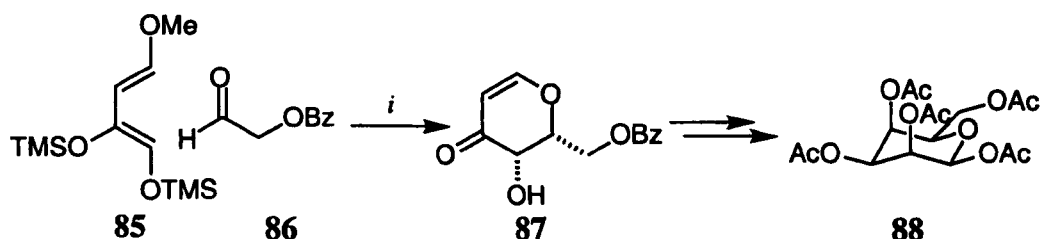
Danishefsky and co-workers have also examined chiral induction in [4+2] cycloadditions of aldehydes to oxygenated dienes bearing chiral auxiliaries.^{71d} Optically

inactive europium(III) catalysis proved effective in promoting the cycloaddition reaction but did not give favourable diastereomer ratios. However, combination of the chiral diene (**81**) with a chiral lanthanide catalyst and reaction with benzaldehyde (**82**) provided the reinforcement needed to generate one diastereomer of the dihydropyran (**84**) in large excess (**Scheme 15**).



Scheme 15

This methodology has been extensively applied towards the total synthesis of several natural products by the Danishefsky group,⁷² providing a pathway to several types of carbohydrates. One example is the monosaccharide *L*-talose (**88**), which was prepared in just a few steps using a hetero Diels-Alder reaction between the aldehyde (**86**) and the diene (**85**) to give the dihydropyrone (**87**), which was subsequently converted to the natural product (**Scheme 16**).^{71a}

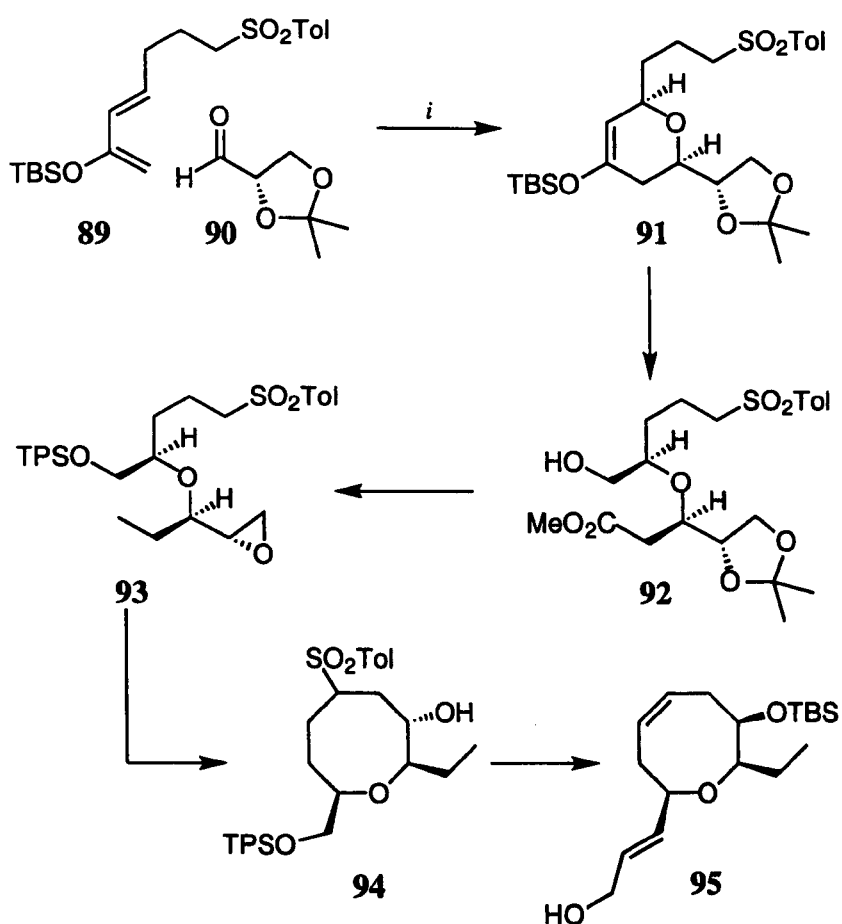


Reagents: *i*, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , 42%.

Scheme 16

The use of the hetero Diels-Alder reaction is not limited to the formation of natural products containing six-membered ring ethers. Upon formation of the [4+2] cycloadduct these can be transformed to a linear ether bearing the stereochemistry inferred from the hetero Diels-Alder reaction. Thus, this reaction can be implemented as

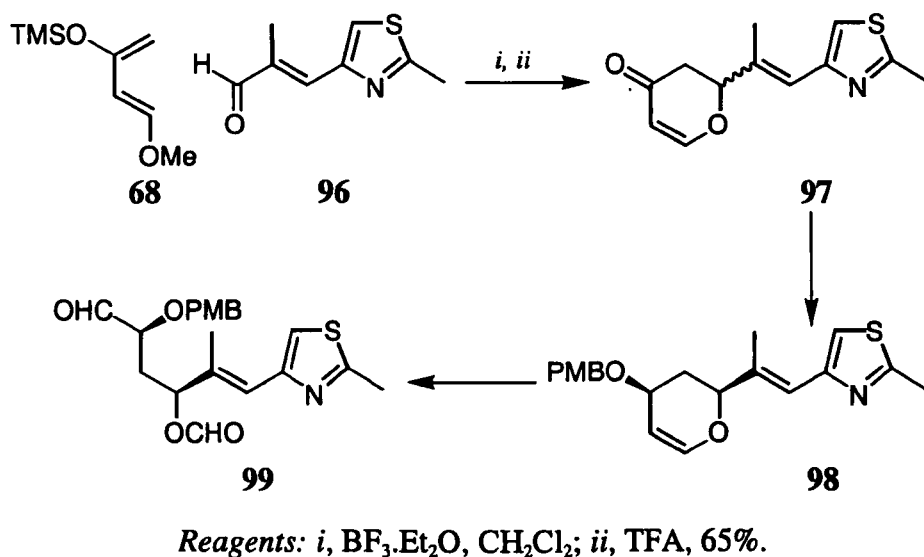
a template for the formation of many stereocentres in a controlled fashion. Palenzuela *et al* have employed this approach for the preparation of α,α' -disubstituted cyclic ethers of various ring sizes.⁷³ The utility of this approach has been shown in their formal synthesis of laurencin (**Scheme 17**).^{73b} An *endo*-Cram hetero Diels-Alder reaction between the diene (**89**) and (*S*)-glyceraldehyde acetonide (**90**) gave the dihydropyran (**91**) in 82% yield and 88:12 ratio favouring the diastereomer shown. Having now provided the two asymmetric centres, which will form the α,α' -positions of the oxocene, Palenzuela *et al* cleaved the olefinic unit in **91** with ozone to give an acyclic ether. Further manipulations eventually gave the oxocene (**95**), which constituted a formal synthesis of laurencin.^{73b}



Reagents: *i*, BF₃·Et₂O, Et₂O, 82%.

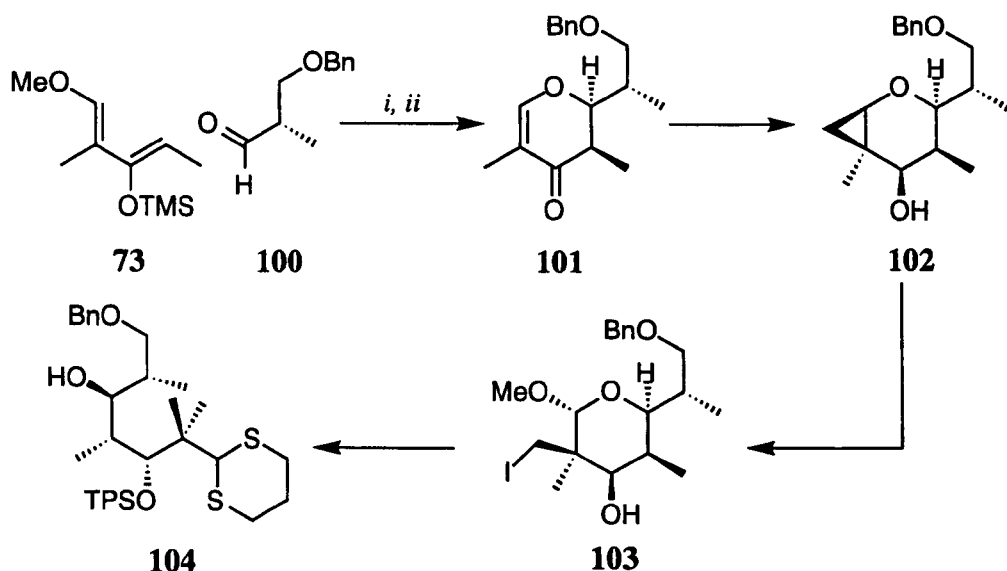
Scheme 17

Danishefsky *et al* have also made extensive use of the hetero Diels-Alder reaction to form dihydropyran templates for the stereocontrolled construction of two fragments used in their total synthesis of epothilone A and B.⁷⁴ Thus, a Lewis acid mediated hetero Diels-Alder reaction of the aldehyde (**96**) with Danishefsky's diene (**68**) gave, after mild acid hydrolysis, the dihydropyran (**97**). The racemic dihydropyran (**97**) was subsequently resolved and then converted into the acyclic aldehyde (**99**), containing the requisite stereocentres, in a short sequence of steps (Scheme 18).^{75a}



Scheme 18

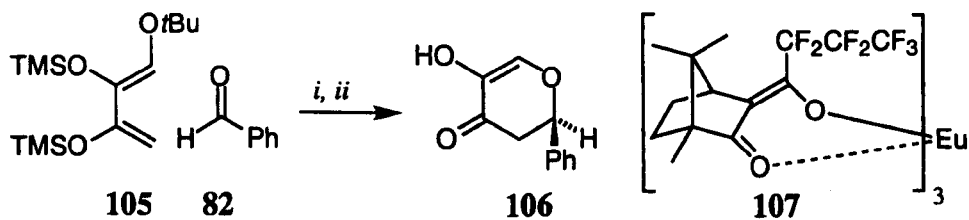
The second fragment synthesised by Danishefsky *et al* used a similar approach, but relied on the chiral aldehyde (**100**) as the stereocontrol element.^{75b} Thus, hetero Diels-Alder reaction between the aldehyde (**100**) and the more complex diene (**73**) gave rise to the dihydropyrone (**101**) in excellent yield and high selectivity. Installation of the geminal methyl group was achieved by cyclopropanation and ring opening, giving rise to the mixed methyl ketal (**103**), which could then be unmasked leading to the acyclic fragment (**104**) bearing four chiral centres, all installed in a highly selective manner (Scheme 19).



Reagents: *i*, TiCl₄, CH₂Cl₂; *ii*, TFA, CH₂Cl₂, 87%.

Scheme 19

The most significant development in recent years however, has been the application of chiral Lewis acids to the hetero Diels-Alder reaction to provide pyrans with high enantiomeric excess directly.⁷⁶ The ready availability of optically active NMR lanthanide shift reagents first led Danishefsky *et al* to investigate the possibility of inducing absolute chirality in these cycloadditions.⁷⁷ Employing Eu(hfc)₃ (**107**) as the catalyst they were able to induce modest (20-50%) enantiomeric excesses (ees), depending on the diene used and the reaction conditions (**Scheme 20**).



Reagents: *i*, Eu(hfc)₃, CHCl₃; *ii*, TFA.

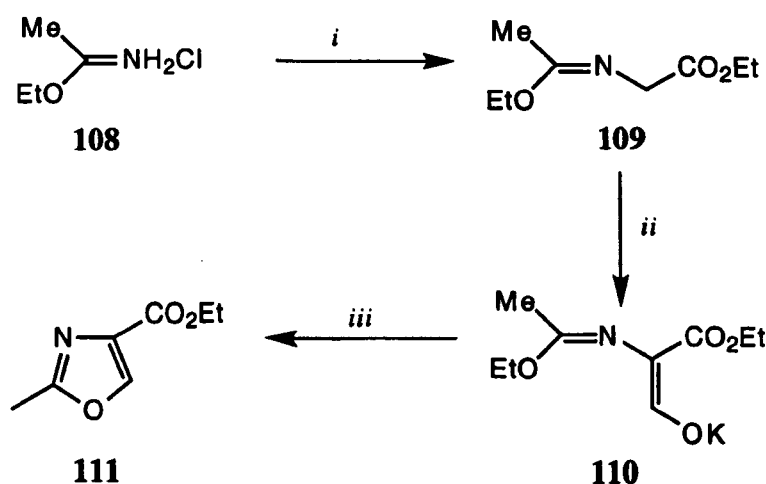
Scheme 20

Many research groups have since contributed towards this asymmetric variant, employing a vast array of conceptually different Lewis acids, to achieve ees in excess

of 90%.⁷⁸ In most cases however, substrate structure and reaction conditions have a large influence on the degree of enantioselectivity.

2.1.3 Initial Hetero Diels-Alder Approaches

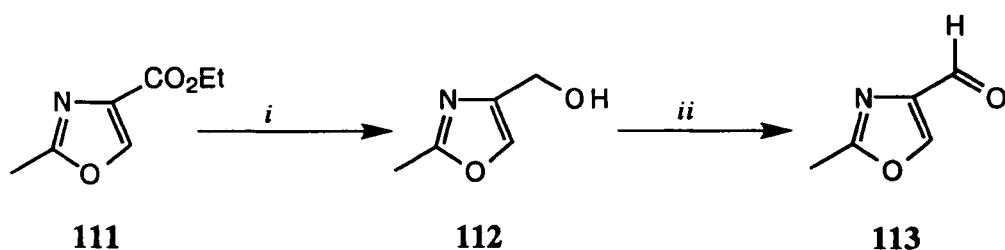
It was our initial intention to examine whether a 4-formyl oxazole (*cf.* **113**) would participate as the dienophile in a [4+2] cycloaddition with an appropriate diene to give rise to a pyran moiety which could be elaborated subsequently to the 2,6-*cis*-pyran present in the phorboxazoles. As this was to be a simple model study at this time, we made use of the Cornforth oxazole, ethyl 2-methyloxazole-4-carboxylate (**111**). The procedure of Cornforth,⁷⁹ employing some modifications developed by Meyers,⁸⁰ provided large quantities of the desired oxazole (**111**) quite readily. Thus, condensation between ethyl acetimidate hydrochloride (**108**) and glycine ethyl ester hydrochloride first gave the imidate (**109**) in 50% yield. The imidate (**109**) was next formylated using the improved procedure of Meyers (*K*^tBuO / HCO₂Et) to provide the enolate salt (**110**) which was then cyclised immediately to the oxazole ester (**111**) by refluxing in acetic acid in a yield of 55% over the two steps (**Scheme 21**).



Reagents: *i*, glycine.OEt.HCl, K₂CO₃, Et₂O, H₂O, 50%; *ii*, *K*^tBuO, HCO₂Et, THF; *iii*, AcOH, Δ, 55% (2 steps).

Scheme 21

The required 4-formyl oxazole (113) was secured by a two step procedure, involving reduction of the ester (111) to the alcohol (112) with 2.5 equivalents of DIBAL-H, followed by oxidation of the alcohol with manganese dioxide to give the aldehyde (113) in good overall yield (Scheme 22).

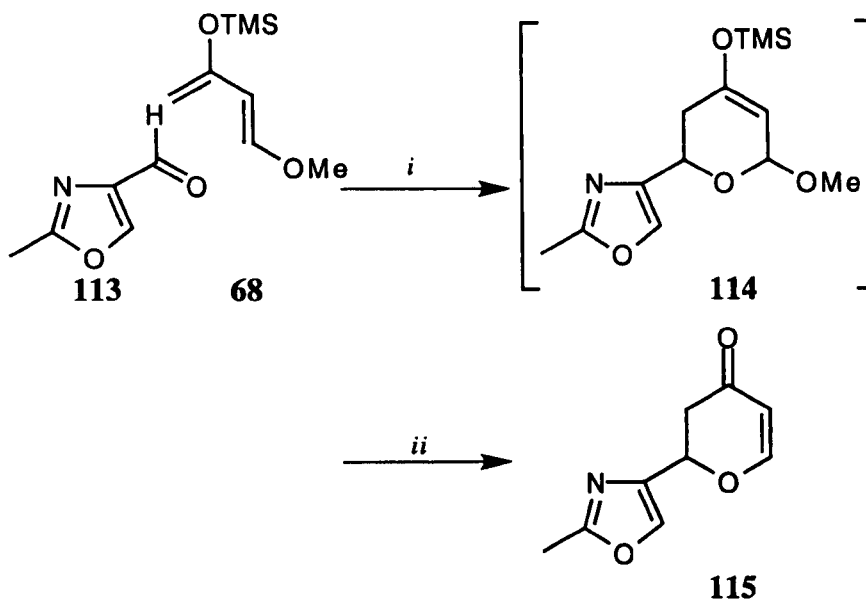


Reagents: *i*, DIBAL-H, CH₂Cl₂, 86%; *ii*, MnO₂, CH₂Cl₂, 85%.

Scheme 22

We were now in a position to examine the hetero Diels-Alder reaction and we initially chose to use the commercially available Danishefsky's diene, *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (68). Danishefsky *et al* had previously shown that α,β -unsaturated aldehydes reacted with this diene (68) under Lewis acid catalysis to give γ -pyrones rather than carbocyclic adducts.⁸¹ With this in mind we anticipated that a 4-formyl oxazole would undergo this [4+2] cycloaddition to give a 2-oxazole substituted 2,3-dihydro- γ -pyrone. This system was attractive to us as it provided functionality for nucleophilic attack at the C-6 position, in a Michael type reaction, for further elaboration to the macrolide fragment. Thus, treatment of the diene (68) and the aldehyde (113) with zinc chloride in benzene gave the desired dihydropyrone (115) after brief exposure to trifluoroacetic acid in a satisfactory 76% yield (Scheme 23).

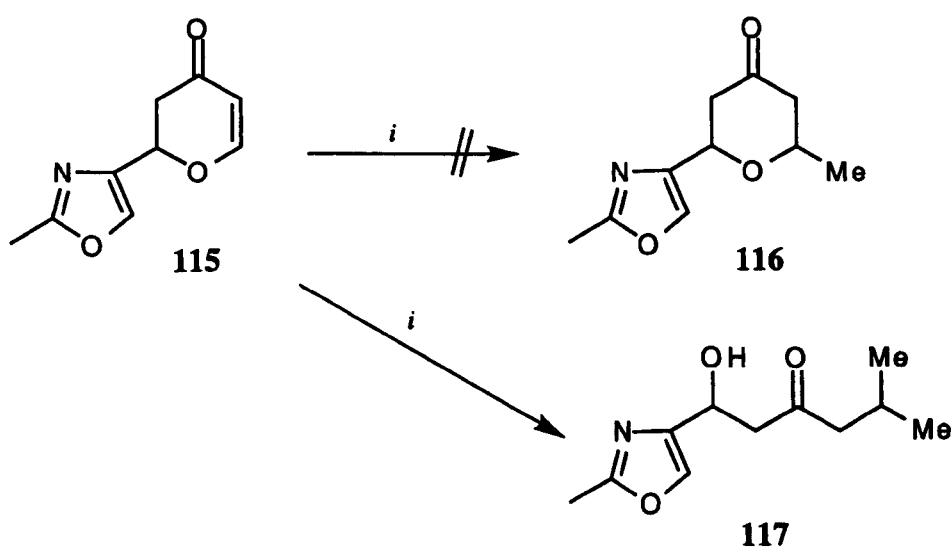
We anticipated that conjugate addition of an alkyl group to the vinylogous ester (115) would give rise to the desired tetrahydropyran (116). We were also interested in the level of stereoselectivity we could achieve favouring the requisite *cis*-configuration. Using the cuprate reagent derived from methyl lithium and copper(I) iodide, and adhering to a literature procedure,⁸² we were successful in obtaining a single, new



Reagents: *i*, ZnCl_2 , C_6H_6 ; *ii*, TFA, CH_2Cl_2 , 76% (2 steps).

Scheme 23

product. On analysis of the reaction product we were dismayed to find that although nucleophilic attack had proceeded, it actually gave rise to opening of the pyran, regenerating the α,β -unsaturated carbonyl system which underwent addition of a second equivalent of the cuprate reagent, to generate the 1,3-hydroxy ketone (117) (Scheme 24).

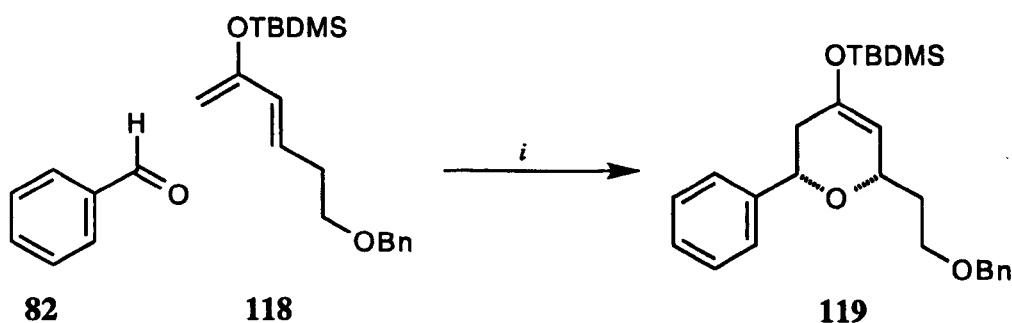


Reagents: *i*, CuI , MeLi , Et_2O , 64%.

Scheme 24

We anticipated that by only using one equivalent of cuprate reagent the intramolecular ring closure would predominate so as to re-form the pyrone system. Treatment of dihydropyrone (**115**) with one equivalent of dimethylcuprate failed to deliver any isolable product, and instead only starting material or decomposition products were observed. Similar observations were made with the cuprate reagent derived from copper(I) bromide and methyl magnesium bromide.

Rather than overcome this problem and the issue of stereoselectivity, we decided to make use of a timely publication by Palenzuela *et al.*⁸³ Palenzuela *et al* studied the effect of various Lewis acids on the reaction of 2-monoactivated dienes and aldehydes in search of more general reaction conditions for the hetero Diels-Alder reaction than those previously published. They found that boron trifluoride diethyl etherate in diethyl ether gave the highest yields of hetero Diels-Alder adducts, with good *endo:exo* selectivity. With benzaldehyde (**82**) and the diene (**118**), the hetero Diels-Alder adduct (**119**) was prepared in 86% yield as a 6:1 ratio of *cis:trans* isomers (Scheme 25).

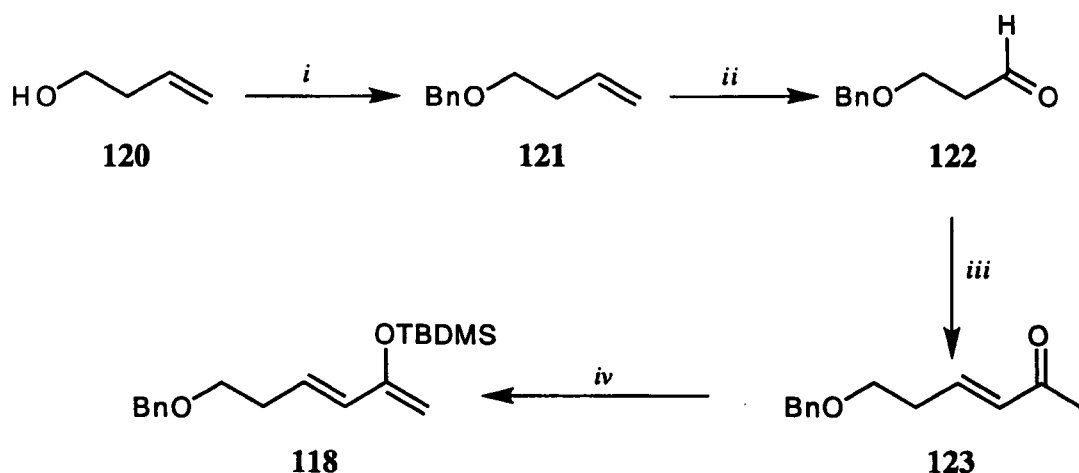


Reagents: *i*, BF₃·Et₂O, Et₂O, 86%.

Scheme 25

The diene (**118**) has the advantage over Danishefsky's diene in that once the pyran is formed no Michael addition step is required. This diene (**118**) also uses the more robust *tert*-butyldimethylsilyl group to trap the enol ether and so unlike that with Danishefsky's diene the [4+2] cycloaddition product is isolated and reasonably stable. We have developed a more efficient route to the diene (**118**) described by Palenzuela,⁸³

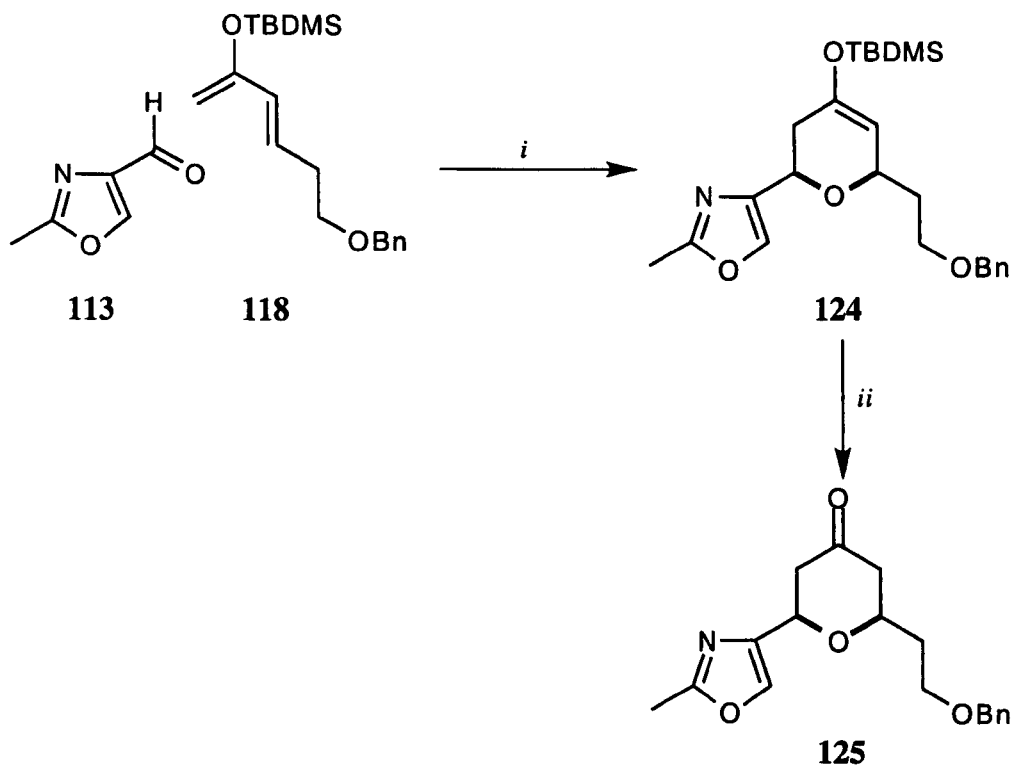
employing a highly selective Wittig reaction. 3-Buten-1-ol (**120**) was protected as the benzyl ether (**121**) and then cleaved to the corresponding aldehyde (**122**) with ozone in dichloromethane in 80-90% yield. Wittig reaction of **122** with 1-(triphenylphosphoranylidene)-2-propanone gave a 27:1 ratio of *E*:*Z* isomers, which could be separated readily by flash chromatography to give the (*E*)- α,β -unsaturated ketone (**123**) in over 90%. Formation of the diene (**118**) was achieved using triethylamine and *tert*-butyldimethylsilyl triflate in quantitative yield (Scheme 26).



Reagents: *i*, NaH, Bu₄NI, Bn-Br, THF, 98%; *ii*, a) O₃, CH₂Cl₂; b) PPh₃, 90%; *iii*, 1-(triphenylphosphoranylidene)-2-propanone, CH₂Cl₂, 90%; *iv*, Et₃N, TBDMS-OTf, CH₂Cl₂, 100%.

Scheme 26

We once again employed our model oxazole aldehyde (**113**) to demonstrate the potential of this hetero Diels-Alder reaction, at this stage not being concerned with enantioselectivity. Using the conditions of Palenzuela,⁸³ reaction of the diene (**118**) with the aldehyde (**113**) mediated by boron trifluoride diethyl etherate at -78°C, gave the desired cycloadduct (**124**) exclusively as a single diastereomer in a modest 60% yield. Exposure of the silyl enol ether (**124**) to TBAF led smoothly to the 4-pyrone (**125**) in 70% yield (Scheme 27).



Reagents: *i*, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, Et_2O , 60%; *ii*, TBAF, THF, 70%.

Scheme 27

Determination of the stereochemical outcome of this hetero Diels-Alder reaction was made by NOE studies. A 10.3% NOE was observed at H-6 upon irradiation of the H-2 proton of the 4-pyrone (125), thus confirming the *cis*-configuration (**Figure 1**). Furthermore, this demonstrates that if the hetero Diels-Alder reaction is concerted, then as expected it passes through an *endo* transition state.

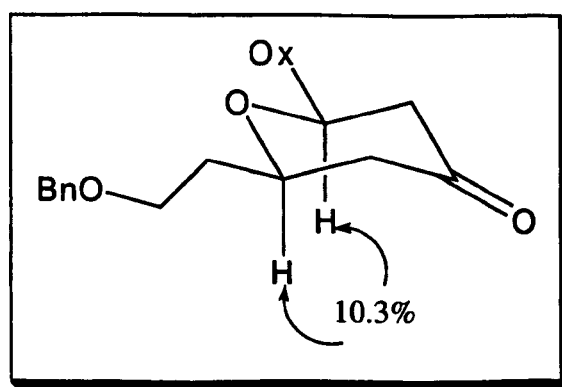
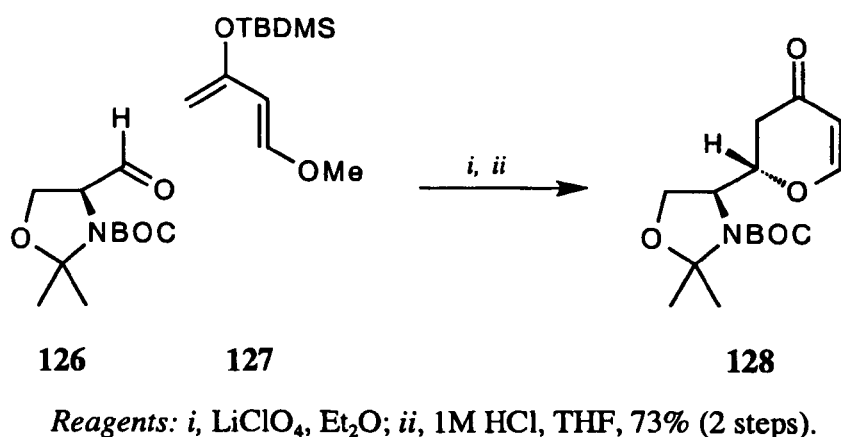


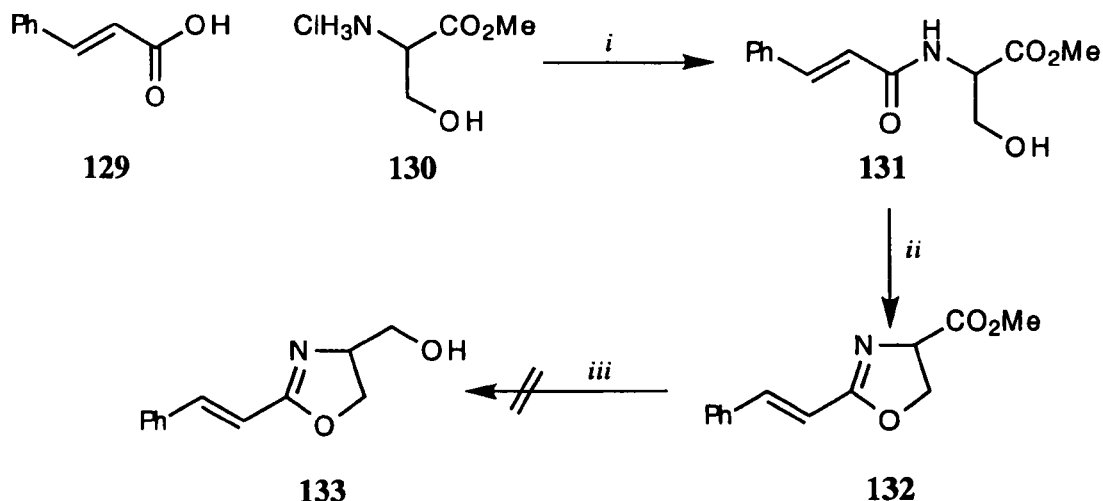
Figure 1: NOE analysis of the pyrone (125).

Gratified by this result we then focused on a route towards controlling the absolute stereochemistry of the pyran ring adjacent to the oxazole. We anticipated that by making use of a chiral oxazoline, the pyran could be formed stereoselectively *via* a hetero Diels-Alder approach. Grieco *et al*⁸⁴ had shown that hetero Diels-Alder adducts can be formed with good diastereoselectivity from *N*-BOC protected α -amino aldehydes. The best result came from the *N*-BOC oxazolidine aldehyde (**126**), also known as Garner aldehyde,⁸⁵ and *trans*-1-methoxy-3-[(*tert*-butyldimethylsilyl)oxy]-1,3-butadiene (**127**) resulting in a 10:1 ratio of dihydropyrans in favour of the *threo* isomer (**128**) (**Scheme 28**). The formation of major adducts possessing the *threo* configuration as exhibited by **128** is consistent with a chelation controlled process.



Scheme 28

We proceeded to make the oxazoline (**132**) derived from cinnamic acid (**129**) and serine methyl ester hydrochloride (**130**) by amide formation followed by a DAST mediated cyclisation.⁸⁶ The amide (**131**) was prepared using standard peptide coupling reagents in 78% yield. Subsequent cyclisation using DAST afforded the oxazoline (**132**) in an excellent 86% yield. We anticipated that reduction of the oxazoline ester (**132**) to the alcohol (**133**) with DIBAL-H would be straightforward; however on all occasions only decomposition products were observed (**Scheme 29**).

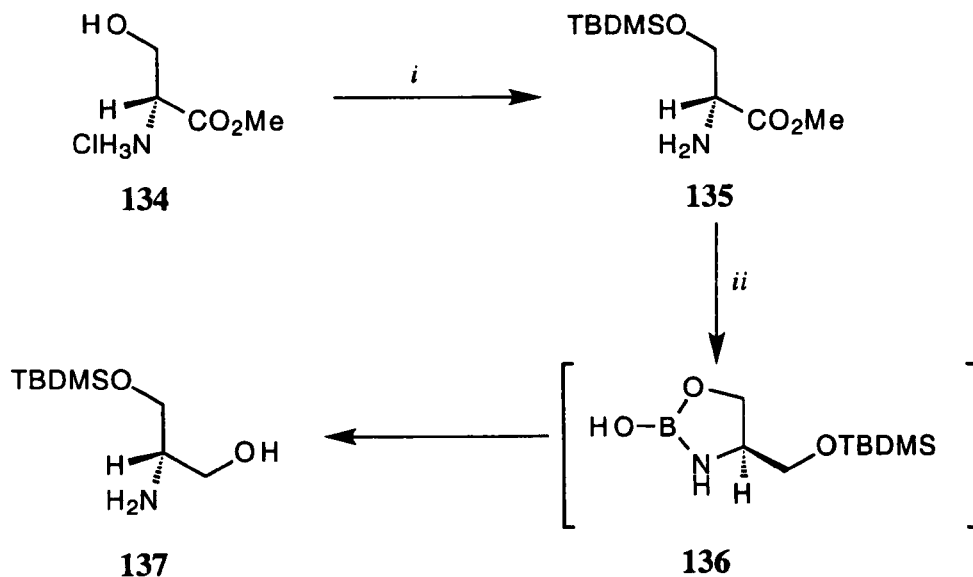


Reagents: *i*, DCC, HOBT, Et₃N, THF, 78%; *ii*, DAST, CH₂Cl₂, 86%; *iii*, DIBAL-H, CH₂Cl₂.

Scheme 29

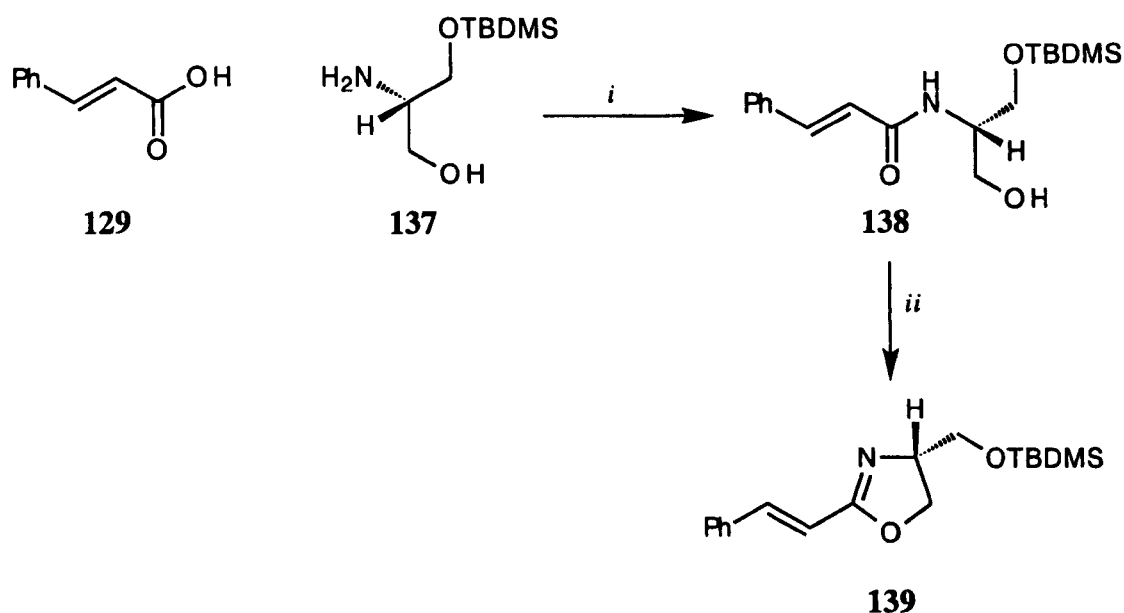
We attributed this failure to the conjugated nature of the oxazoline and so decided to reduce serine methyl ester prior to coupling and cyclisation, thus avoiding the problematic reduction step. Furthermore it has been shown that the enantiomeric purity of hydroxymethyl oxazolines has been found to vary due to racemization during the reduction.⁸⁷ We were able to prepare the amino alcohol (137) in two steps from *d*-serine methyl ester hydrochloride (134) according to the procedure of Meyers.⁸⁷ *d*-Serine methyl ester hydrochloride (134) was liberated to the free amine and then treated with *tert*-butyldimethylsilylchloride and imidazole to furnish the corresponding silyl ether (135) in 99% yield. The ester (135) was then reduced using sodium borohydride in methanol at 35°C to give the free amino alcohol (137) in 80% yield after treatment with pH 4 buffer to hydrolyse any boronate ester (136) present (**Scheme 30**).

Coupling of the TBDMS protected amino alcohol (137) with cinnamic acid (129) was achieved in a 75% yield leading to the amide (138) which was cyclised subsequently with DAST to afford the corresponding oxazoline (139) in a satisfactory 77% yield (**Scheme 31**).



Reagents: i, a) Et₃N, CH₂Cl₂; b) TBDMS-Cl, Im., 99%; ii, NaBH₄, MeOH, pH 4 Buffer, 80%.

Scheme 30

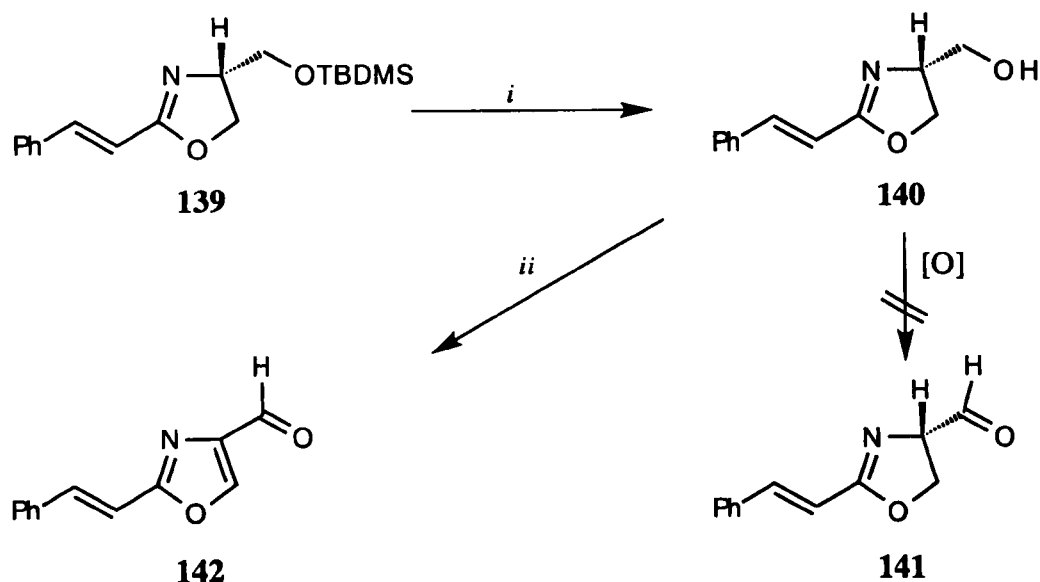


Reagents: i, DCC, HOBT, NMM, THF, 75%; ii, DAST, CH₂Cl₂, 77%.

Scheme 31

With the oxazoline (139) in hand we only needed to deprotect the silyl ether, followed by oxidation to obtain our desired chiral aldehyde. Deprotection of the silyl ether (139) to give the alcohol (140) was accomplished with TBAF in 88% yield. Unfortunately,

we were unable to isolate any of the chiral oxazoline aldehyde (**141**) under various oxidation conditions including; Swern,⁸⁸ pyridine sulfur trioxide modification of the Swern reaction,⁸⁹ Dess-Martin periodinane⁹⁰ or manganese dioxide. Most notably under Swern conditions over-oxidation to the oxazole aldehyde (**142**) was observed in 60% yield (Scheme 32).

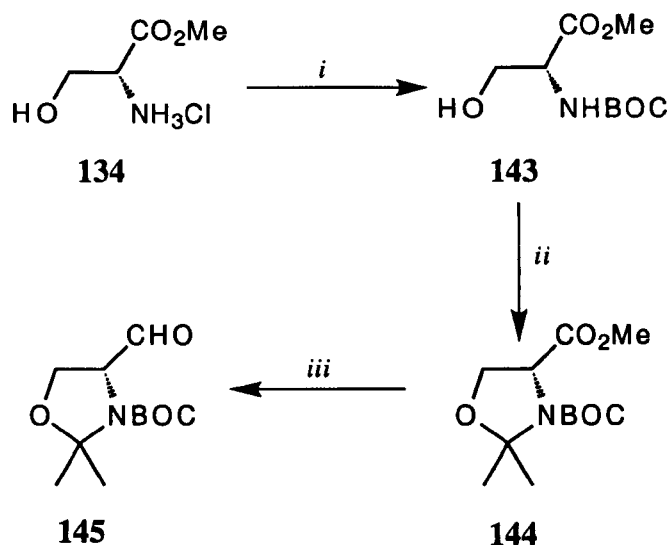


Reagents: *i*, TBAF, THF, 88%; *ii*, (COCl)₂, DMSO, Et₃N, CH₂Cl₂, 60%.

Scheme 32

Disappointed by our inability to prepare the desired oxazoline aldehyde (**141**), we considered the use of Garner aldehyde (**145**)⁸⁵ which we anticipated could be elaborated to the desired oxazole subsequent to the hetero Diels-Alder step. The Garner aldehyde (**145**) can be prepared in excellent yield with high enantiomeric excess in three steps from *d*-serine methyl ester hydrochloride (**134**) using the modified procedure of Taylor *et al* (Scheme 33).⁹¹

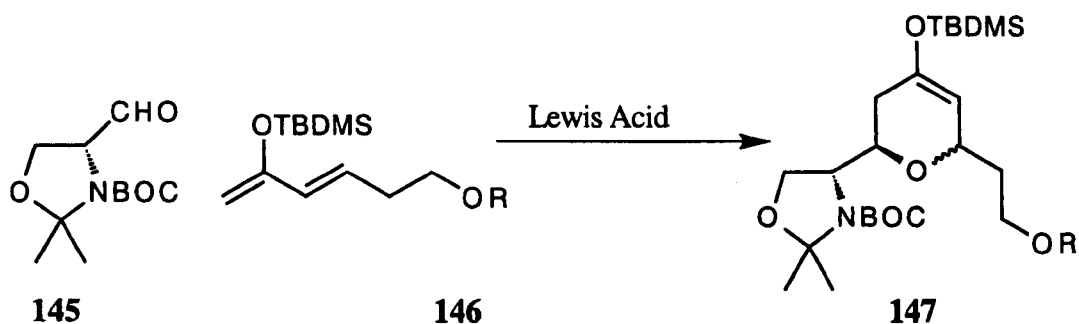
The carbamate (**143**) was routinely obtained in 90% yield from *d*-serine methyl ester hydrochloride (**134**) by treatment with di-*tert*-butyl dicarbonate in THF and triethylamine. Treatment of **143** with 2,2-dimethoxypropane and boron trifluoride diethyl etherate in acetone at room temperature gave the oxazolidine (**144**) in 88%



Reagents: i, BOC₂O, Et₃N, THF, 90%; ii, 2,2-DMP, BF₃.Et₂O (cat.), acetone, 88%; iii, DIBAL-H, toluene, 80%.

Scheme 33

yield. Subsequent reduction of the ester (144) with DIBAL-H in toluene at -78°C afforded the aldehyde (145) in 80% yield. We anticipated that this aldehyde (145) would undergo a facile hetero Diels-Alder reaction with the diene (146), through a similar chelation-controlled reaction as described by Grieco,⁸⁴ to give the cycloadduct (147) stereoselectively (Scheme 34).



Scheme 34

We have shown that cycloadducts from 2-methyl-4-formyl oxazole (113) and dienes of this type (146) can be achieved in good yield. However, with the Garner aldehyde (145) only low yields of cycloadduct were obtained initially. We extensively examined

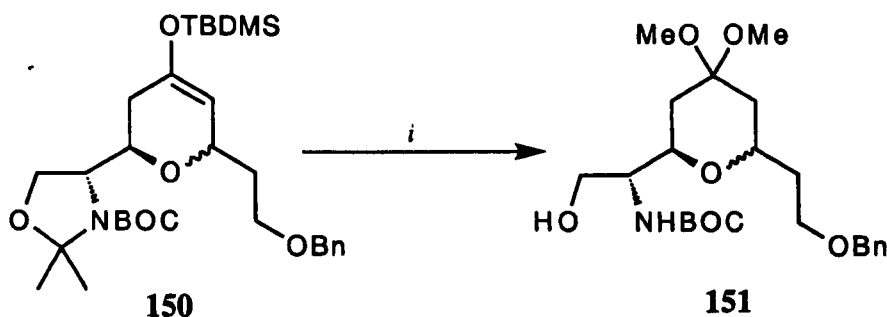
this reaction and were able to achieve a yield of 65% with good stereoselectivity using zinc chloride in hexane (**Table 1**).

Aldehyde	Diene	Conditions	Yield (%)	Stereoselectivity
145	148 R = TBDPS	LiClO ₄ /Et ₂ O ^a	0	-
145	118 R = Bn	BF ₃ .Et ₂ O/Et ₂ O ^a	31	√
145	118 R = Bn	BF ₃ .Et ₂ O/THF ^c	0	-
145	118 R = Bn	ZnCl ₂ /Benzene ^a	35	√
145	118 R = Bn	ZnCl ₂ /Et ₂ O ^a	25	√
145	118 R = Bn	ZnCl ₂ /Hexane ^c	65	√
145	118 R = Bn	Et ₂ AlCl/Hexane ^b	55	x
145	149 R = PMB	ZnCl ₂ /Hexane ^c	65	√
145	149 R = PMB	ZnCl ₂ /CH ₂ Cl ₂ ^d	31	√

Relative to 1eq. of diene: **a** 1.4eq. aldehyde, 1eq. Lewis acid; **b** 1.5eq. aldehyde, 1.5eq. Lewis acid; **c** 1.5eq. aldehyde, 1eq. Lewis acid; **d** 1.5eq. aldehyde, 2eq. Lewis acid.

Table 1

We were unable to determine the diastereoselectivity of the hetero Diels-Alder reaction directly by ¹H or ¹³C NMR as all the cycloadducts existed as rotameric species. By removal of the acetonide in **150** with PTSA in methanol (**Scheme 35**), the dimethyl ketal (**151**) was formed in 80%.



Reagents: *i*, PTSA, MeOH, 80%.

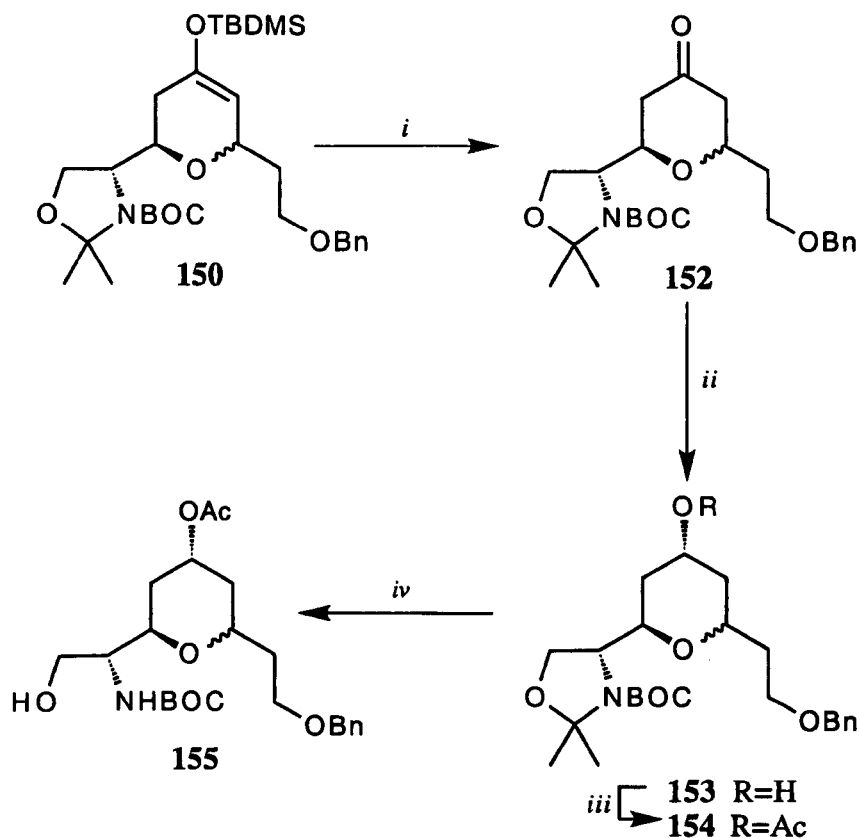
Scheme 35

Examination of the ^1H NMR spectra of the ketal derivatives was not very informative. However the derivatives no longer existed as rotameric species. The ^{13}C NMR spectra proved to be far more useful, and the dimethyl ketal from the hetero Diels-Alder reaction with diethylaluminium chloride clearly showed two sets of peaks of similar intensities. With the other Lewis acids only one set of peaks were observed in the ^{13}C NMR spectra, indicating the presence of a single diastereomer, though at this stage we could not determine whether we had a *cis*- or *trans*-pyran from the hetero Diels-Alder reaction. Now satisfied that some degree of asymmetric induction had been achieved, we continued to elaborate the dihydropyran (**150**) to the oxazole-pyran fragment and to establish the stereochemistry *en route*.

It was our intention to obtain the alcohol from the Diels-Alder adduct (**150**) by hydrolysis and selectively reducing the ketone (**152**) to the axial alcohol using K-selectride[®]. We deemed it necessary to reduce the ketone (**152**) at this stage in order to prevent any elimination to the dihydropyran under the conditions required later for oxazole formation.

Desilylation of the silyl enol ether (**150**) was achieved in 95% yield with TBAF to give the ketone (**152**), which was then reduced with K-selectride[®] leading to a 5:1 ratio of isomers of the corresponding alcohol (**153**) in 80% overall yield. Subsequent acetylation under standard conditions gave the acetate (**154**) in quantitative yield. The acetonide group was then cleaved by exposure to acidic methanol to furnish **155** in 80% yield (Scheme 36).

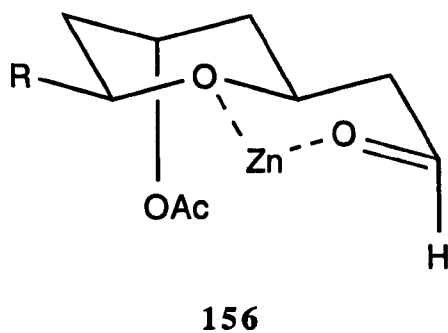
Our next intention was to examine possible routes for the formation of the second adjacent pyran ring in phorboxazole A (**4**). The *trans*-stereochemistry of this pyran presents a far more challenging problem, and possible approaches would involve many additional steps with the need for the control of several newly formed chiral centres. A



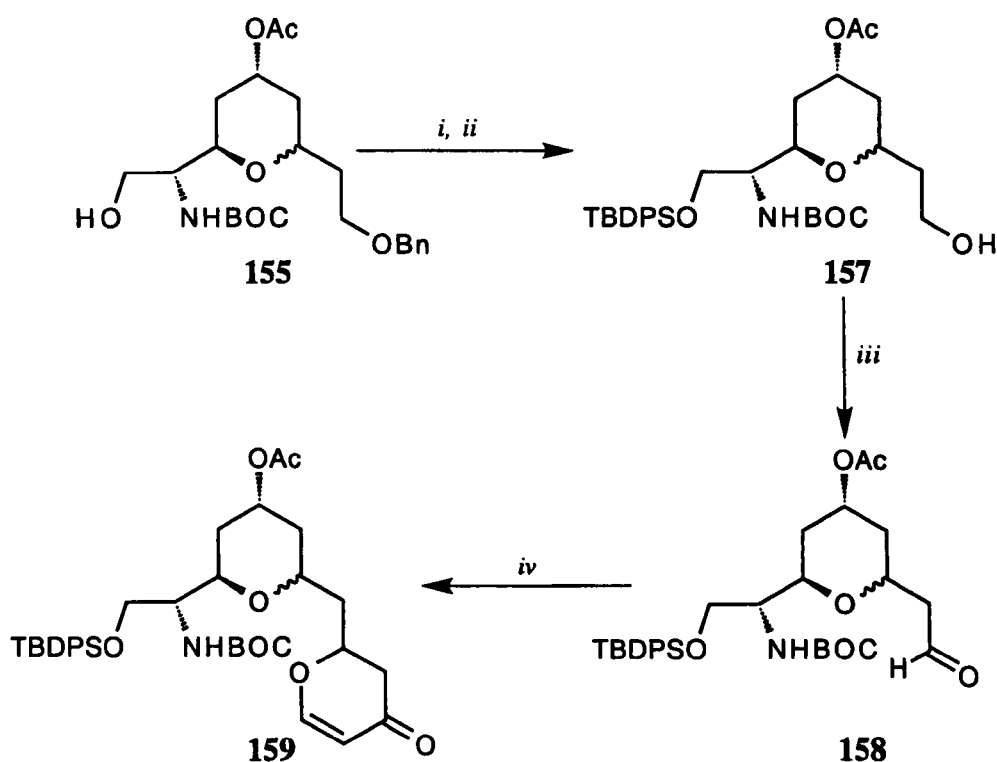
Reagents: *i*, TBAF, THF, 95%; *ii*, K-selectride[®], THF, 80%; *iii*, Ac₂O, Py., DMAP (cat.), 100%; *iv*, PTSA, MeOH, 80%.

Scheme 36

number of possible pyran ring closure protocols were available. One such approach was a second hetero Diels-Alder reaction with Danishefsky's diene (**68**), with the possibility that β -chelation control would be inferred through a chelate such as **156**.



We chose to protect the alcohol (**155**) as its TBDPS ether and use this material to examine possible approaches towards the second pyran. This protection was achieved in 92% yield and subsequent hydrogenation of the benzyl group gave the alcohol (**157**) in quantitative yield. Oxidation of this alcohol with pyridine sulfur trioxide, triethylamine and DMSO⁸⁹ next gave the aldehyde (**158**) in 75% yield. The aldehyde (**158**) was then treated with Danishefsky's diene (**68**) in the presence of zinc chloride. After six hours all the aldehyde (**158**) had been consumed, and work up followed by purification by flash chromatography gave a 57% yield of the cycloadduct (**159**) (Scheme 37).



Reagents: i, TBDPS-Cl, Et₃N, DMAP (cat.), CH₂Cl₂, 92%; ii, H₂, Pd/C, MeOH, 100%; iii, Py.SO₃, Et₃N, DMSO, 75%; iv, Danishefsky's diene, ZnCl₂, benzene, 57%.

Scheme 37

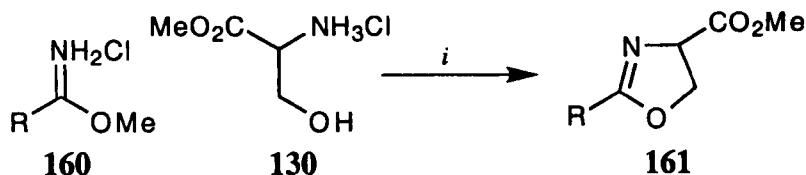
At this stage we were unable to determine whether any diastereoselectivity was being inferred by analysis of the ¹H NMR spectrum. The newly formed stereogenic centre in

159 may be too remote from the pre-existing chiral centres for any diastereomers to be distinguished by ^1H NMR. The ^{13}C NMR spectrum however, displayed an extra signal, which we believe is due to a mixture of diastereomers at the newly formed stereogenic centre in **159**, indicating that no stereochemical induction had been achieved. Also, due to the difficulty in assigning a configuration to this stereogenic centre, we decided not to pursue this route. Instead, we decided to focus on formation of the oxazole prior to the elaboration of the *trans*-pyran.

2.1.4 Oxazole Formation

The widespread occurrence, uses and synthesis of oxazole derivatives have been the subject of extensive reviews.⁹² Because of the many roles that these compounds play in natural product and synthetic organic chemistry, many methods have been developed for their efficient construction. The 2,4-disubstituted oxazole is by far the most common type of oxazole found in natural products and the vast majority of research has been towards those compounds possessing a 4-carboxyl group. Many of these methods also have the flexibility for inclusion of a substituent at the 5-position.

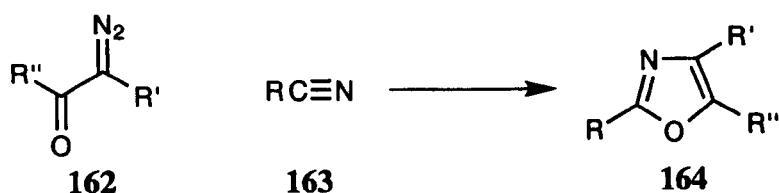
Early methods for oxazole formation focused on the combination of imidates with amino acids, *eg* glycine, followed by addition of ethyl formate and a base, to generate an enolate, which could then form the oxazole by cyclodehydration (see earlier work, **Scheme 21**).⁷⁹ Alternatively, combination of an imidate (**160**) with serine methyl ester hydrochloride (**130**) under mild basic conditions gives rise to an oxazoline (**161**),⁹³ which can subsequently be oxidised to an oxazole (**Scheme 38**).



Reagents: *i*, Et₃N, CH₂Cl₂, 75%.

Scheme 38

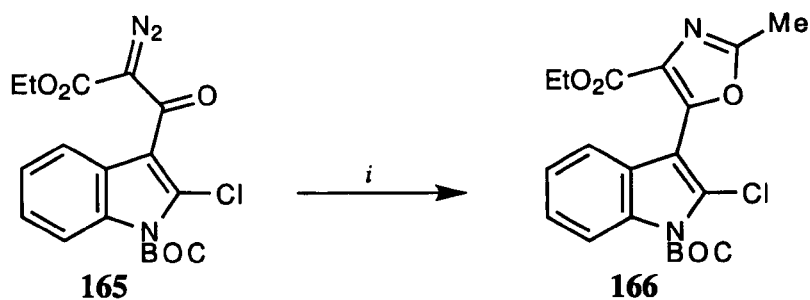
α -Diazocarbonyl compounds (**162**) have also been shown to participate in oxazole formation by undergoing reactions with nitriles (**163**) (Scheme 39).⁹⁴ Reactions of these compounds can be induced either thermally, photochemically, or by metal catalysis. This method can provide oxazoles (**164**) bearing much different, simple functionality, but has not yet been widely applicable towards very complex systems.



Scheme 39

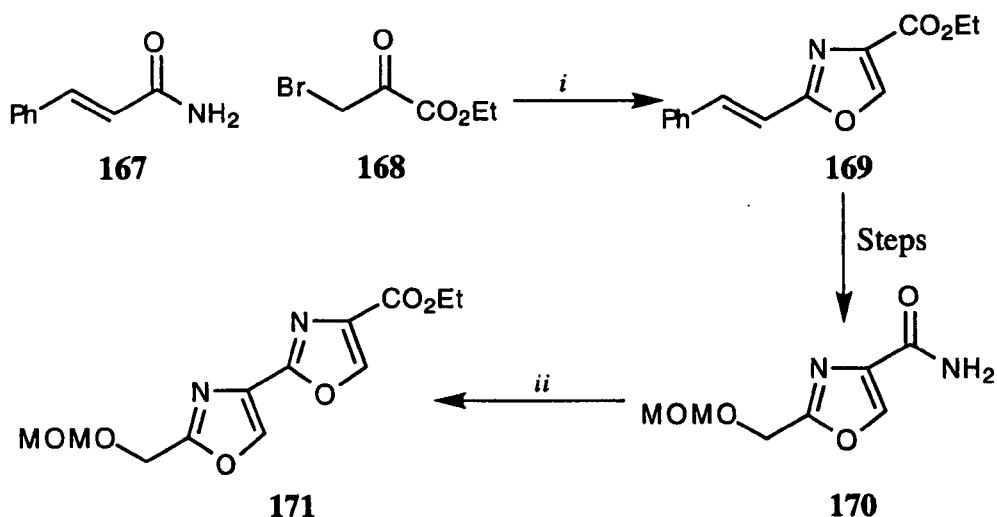
Konopelski *et al* have shown the utility of this reaction in their studies towards diazonamide A (**29**).⁹⁵ Treatment of the α -diazo- β -keto ester (**165**) under Lewis acidic conditions in acetonitrile furnished the desired 2-methyl oxazole (**166**) in 64% yield (Scheme 40). This approach is limited by the need to employ the nitrile as solvent to obtain the best results, and thus limits the functionality that can be incorporated.

An alternative method for oxazole formation is the Hantzsch synthesis,⁹⁶ which has been widely used for the synthesis of thiazoles,⁹⁷ but less so for oxazoles. This method involves condensation of an amide with a halo-keto-ester, giving rise to a 2,4-disubstituted oxazole after acid-mediated dehydration. The utility of this method has recently been demonstrated by Panek *et al*, in their synthesis of the *tris*-oxazole unit of ulapualide A (**31**) (Scheme 41).⁹⁸



Reagents: i, BF₃·Et₂O, CH₃CN, 64%.

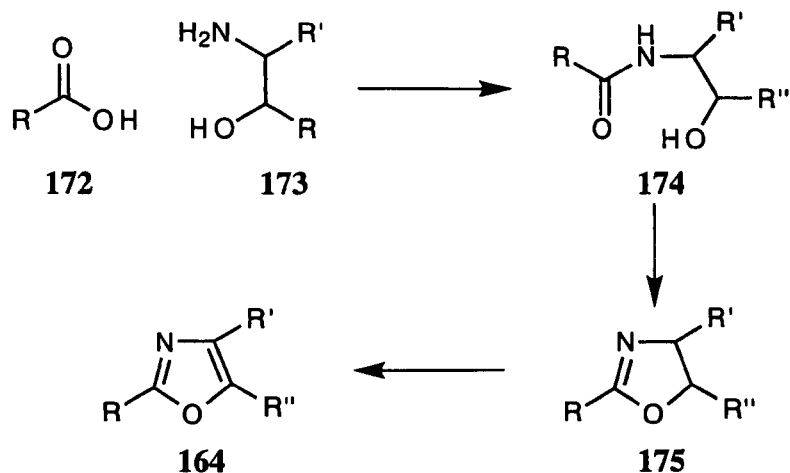
Scheme 40



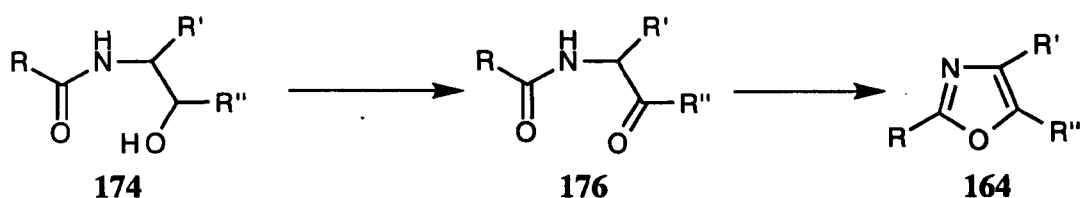
Reagents: i, a) NaHCO₃, Δ; b) TFAA, THF, 83%; ii, a) BrCH₂COCO₂Et (168), NaHCO₃, Δ; b) TFAA, THF, 60%.

Scheme 41

Perhaps the most widely used route towards oxazole formation within highly complex natural products involves amide (174) formation followed either by i) cyclisation to an oxazoline (175) and subsequent oxidation to give the oxazole (164) (Scheme 42) or ii) oxidation to a 1,3-dicarbonyl species (176), followed by cyclodehydration (Scheme 43). These methods allow for the formation of oxazoles with high levels of functionality at each position by the union of corresponding acids and amines to give amides which serve as the oxazole precursors.



Scheme 42



Scheme 43

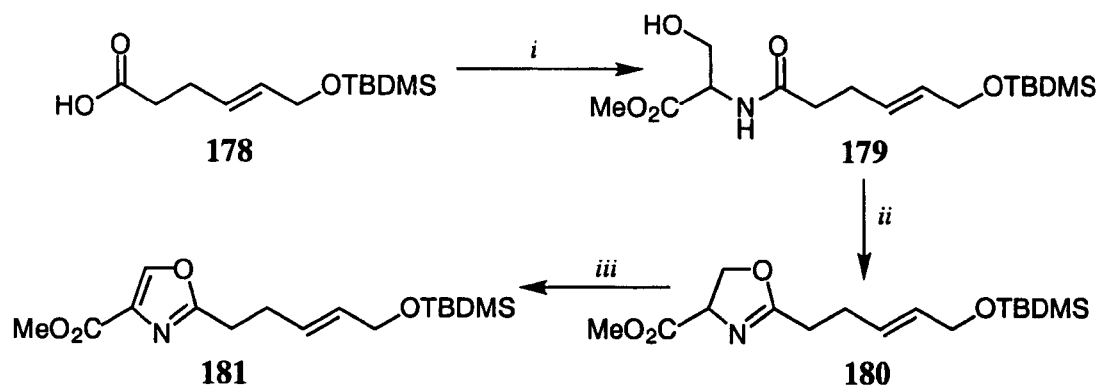
Over recent years many research groups have developed efficient syntheses based on these type of reactions, and a whole variety of reagents and conditions are now available to effect these transformations. Initial formation of the oxazoline can be achieved in many ways. Essentially activation of the hydroxy amide is required for cyclisation to occur. Activation can be promoted by thionyl chloride, followed by treatment with silver triflate;⁹⁹ methanesulfonyl chloride and triethylamine;¹⁰⁰ triphenylphosphine, carbon tetrachloride and DIPEA;¹⁰⁰ under Mitsunobu conditions;¹⁰¹ phosphorus oxychloride;¹⁰² or the more commonly encountered Burgess reagent¹⁰³ or DAST.⁸⁶ Careful considerations must be taken when choosing a suitable reagent for this transformation, as elimination, aziridine formation or epimerisation may also occur.¹⁰⁴

The oxidation protocol has also been developed extensively and in general proceeds by either a radical pathway or an addition-elimination sequence; in either case, the need for

an enolisable group at the 4-position seems necessary to effect this transformation in good yield. Methods that have been examined and shown to be successful include nickel peroxide in refluxing benzene;¹⁰⁵ copper(II) bromide and DBU;¹⁰⁶ copper(I) bromide and *t*-butyl peroxybenzoate;¹⁰⁷ formation of 5-seleno-oxazoles, oxidation and elimination;¹⁰⁸ carbon tetrachloride, pyridine and DBU in acetonitrile,¹⁰⁹ and bromotrichloromethane and DBU.¹¹⁰ Again careful choice of reagent is required for oxidation depending on the substrate.

An alternative pathway developed by Wipf has also proven to be extremely useful in oxazole formation *en route* to natural products. Wipf, having encountered problems with the capricious oxidation of oxazolines to oxazoles, pursued a Robinson-Gabriel type cyclisation of a β -keto amide to furnish an oxazole.¹¹¹ Thus, oxidation of a β -hydroxy amide with the Dess-Martin reagent,⁹⁰ followed by mild cyclodehydration of the intermediate β -keto amide with triphenylphosphine, iodine and triethylamine allowed the rapid synthesis of highly substituted and functionalised oxazoles in good overall yield. Amido-aldehydes derived from serine residues were found to cyclise to the oxazole in a much less facile manner. Wipf overcame this problem by changing the reaction conditions and so used the bulky base 2,6-di-*tert*-butyl-4-methyl pyridine, with dibromotetrachloroethane and triphenylphosphine. Under these conditions elimination did not occur spontaneously and required subsequent treatment with DBU to furnish the oxazole.⁵³

The use of both these approaches is shown by Wipf's total synthesis of the enantiomer of hennoxazole A (**177**).⁵³ Thus, condensation of the acid (**178**) with serine methyl ester hydrochloride (**130**), *via* the mixed anhydride, gave the β -amido alcohol (**179**) which was cyclised to the oxazoline (**180**) with the Burgess reagent.¹⁰³ Oxidation of **180** with copper(II) bromide and DBU then gave the desired oxazole (**181**) in 37% overall yield (Scheme 44).

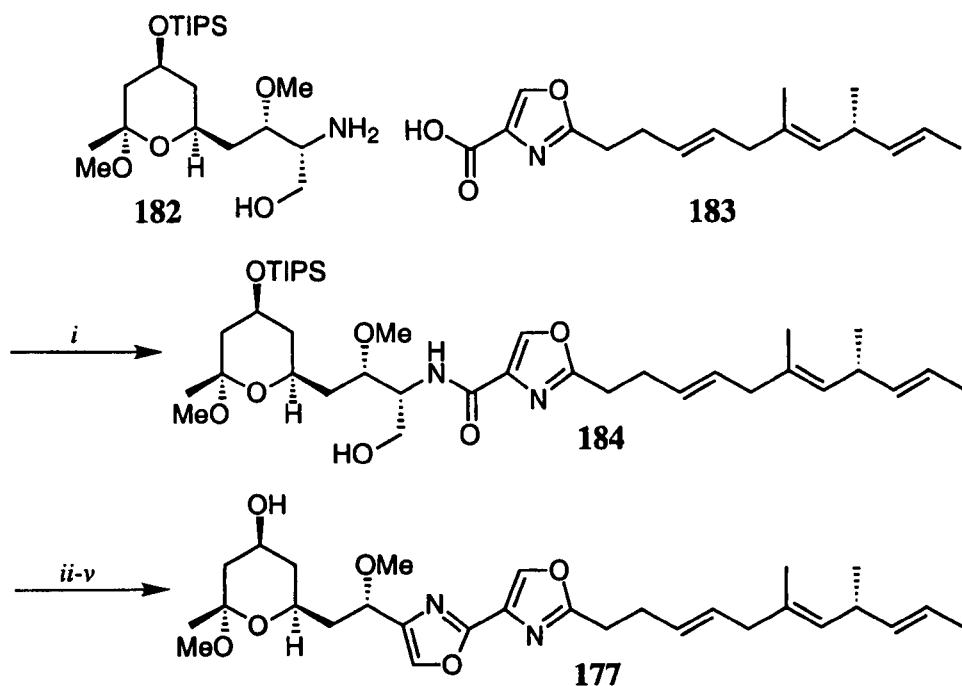


Reagents: *i*, Serine-OMe.HCl, *i*-BuOC(O)Cl, Et₃N, CH₂Cl₂; *ii*, Burgess reagent, THF; *iii*, CuBr₂, DBU, HMTA, CH₂Cl₂, 37% (3 steps).

Scheme 44

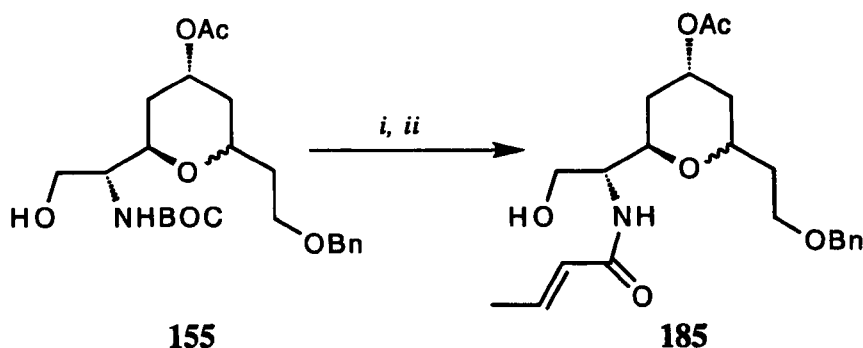
Elaboration of the side chain in **181** and saponification of the ester gave the acid precursor (**183**) to the second oxazole. The acid (**183**) was next coupled to the tetrahydropyran-amine unit (**182**) under standard peptide forming conditions to give the β -amido alcohol (**184**) in 63% yield. Oxidation of **184** with Dess-Martin periodinane then gave the intermediate amido aldehyde, which was smoothly cyclodehydrated using the conditions described previously to give the enantiomer of hennoxazole A (**177**) after desilylation with TBAF in 42% overall yield (Scheme 45).⁵³

Returning to our own system, we were now in a position for *N*-BOC deprotection of the carbamate (**155**) and formation of a suitable amide precursor (**185**) for oxazole formation. We chose crotonic acid to couple with the amine as it was a readily available synthon for a protected alcohol. Once the oxazole has been formed the olefin can then be functionalised by dihydroxylation and diol cleavage. Thus, treatment of the carbamate (**155**) with trifluoroacetic acid in dichloromethane proceeded smoothly to give the corresponding amine which was then treated directly with triethylamine, EDC, HOBT and crotonic acid to give the desired hydroxy amide (**185**) in 68% overall yield (Scheme 46).



Reagents: *i*, PyBroP, DIPEA, CH₂Cl₂, 63%; *ii*, Dess-Martin periodinane, CH₂Cl₂; *iii*, BrCl₂CCl₂Br, PPh₃, 2,6-di-*tert*-butyl-4-methylpyridine, CH₂Cl₂; *iv*, DBU, CH₃CN; *v*, TBAF, THF, 42% (4 steps).

Scheme 45

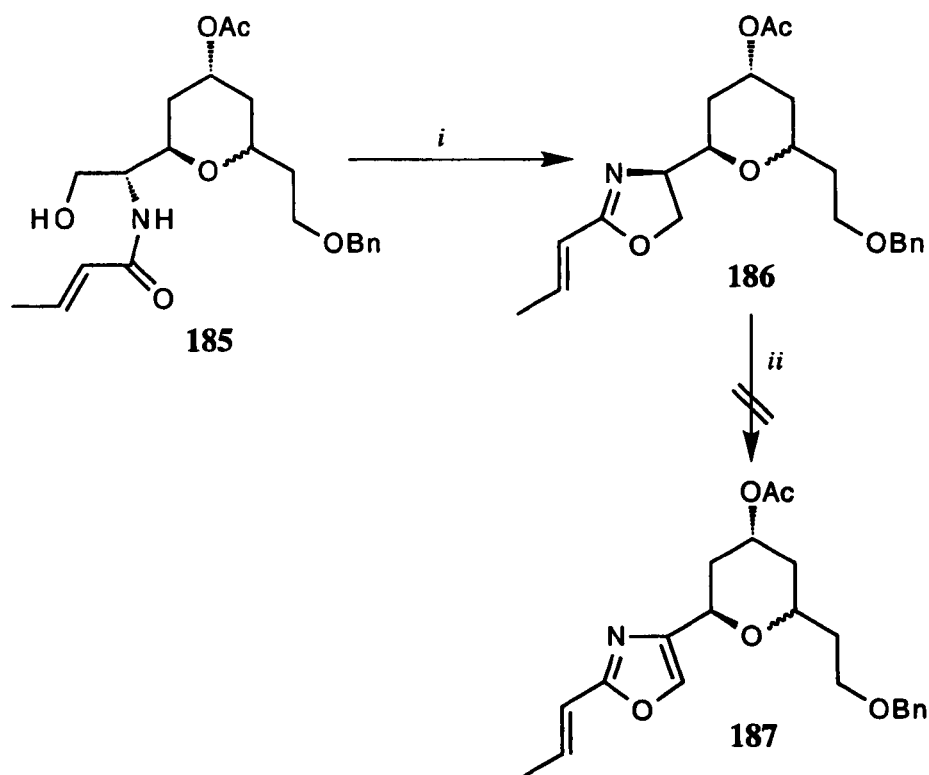


Reagents: *i*, TFA, CH₂Cl₂; *ii*, EDC, HOBT, Et₃N, crotonic acid, THF, 68% (2 steps).

Scheme 46

In view of all the literature methods towards oxazole formation, we anticipated that cyclisation of **185** to the oxazoline (**186**) and subsequent oxidation would furnish the desired oxazole (**187**). Treatment of the β -hydroxy amide (**185**) with DAST⁸⁶ at -78°C yielded, upon aqueous work up, the oxazoline (**186**) in 68% yield. We then attempted

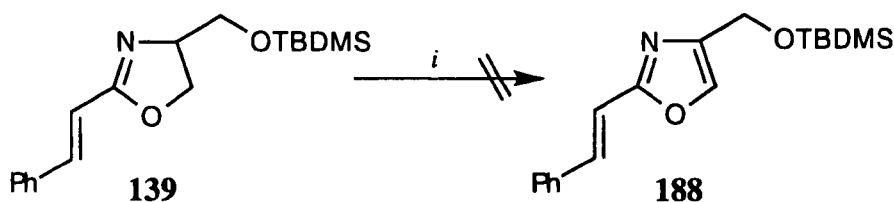
to oxidise **186** to the corresponding oxazole (**187**) using the conditions described by Jung *et al.*,¹⁰⁹ which had previously been used within our research group with success.⁵⁰ However, stirring **186** with DBU, carbon tetrachloride and pyridine in acetonitrile at room temperature for four days provided no evidence of oxazole (**187**) formation; instead only starting material was recovered (**Scheme 47**).



Reagents: i, DAST, CH₂Cl₂, 68%; ii, DBU, CCl₄, Py., CH₃CN.

Scheme 47

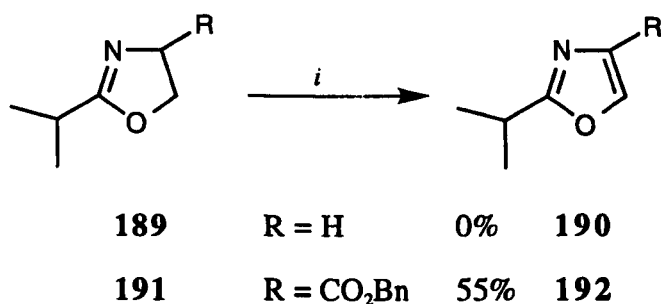
This outcome prompted us to examine a simpler, model oxazoline (**139**) which was synthesised as described previously (**Scheme 31**). Under no circumstances could we prepare the desired oxazole (**188**) using Jung's conditions¹⁰⁹ or nickel peroxide or manganese dioxide in refluxing benzene (**Scheme 48**).¹⁰⁵



Reagents: i, NiO₂ or MnO₂, benzene, Δ.

Scheme 48

In almost all the examples encountered in the literature the need for a 4-carboxyl group or unsaturation at the 4-position to accelerate these oxidations is evident. Barrish and Singh *et al*¹⁰⁶ were unable to oxidise the oxazoline (**189**) to the corresponding oxazole (**190**) under their conditions (CuBr₂, DBU), but with a benzyl ester at the 4-position they achieved a satisfactory yield of the oxazole (**192**). They suggested the intermediacy of a copper(II) enolate reinforcing the need for an enolisable group at the 4-position (**Scheme 49**).



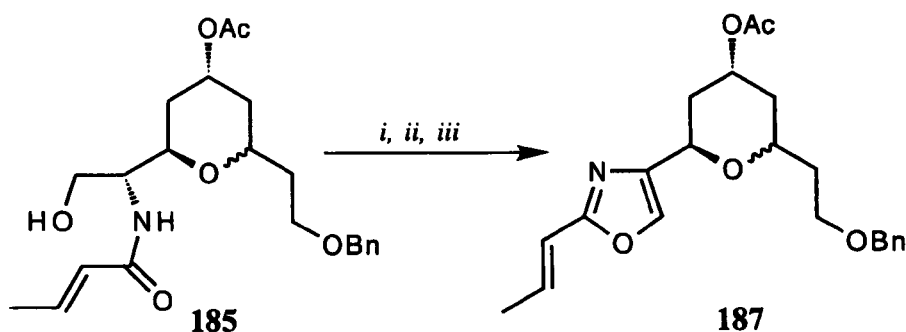
Reagents: i, CuBr₂, DBU, EtOAc, CHCl₃.

Scheme 49

In light of this we decided that the conditions described by Wipf⁵³ (Dess-Martin⁹⁰ oxidation and cyclodehydration with tetrachlorodibromoethane, triphenylphosphine, 2,6-di-*tert*-butyl-4-methylpyridine and DBU) might be useful for obtaining the oxazole (**187**) directly from the hydroxy amide (**185**).

Thus, we decided to apply these conditions to our own system. Oxidation of the amido alcohol (**185**) proceeded smoothly with Dess-Martin periodinane,⁹⁰ to give the

corresponding amido aldehyde. After filtration of the reaction mixture through a short column of silica, the aldehyde was cyclised directly to the bromo-oxazoline with tetrachlorodibromoethane, triphenylphosphine and 2,6-di-*tert*-butylpyridine. Without further purification, dehydrohalogenation (DBU, CH₃CN) of the intermediate bromo-oxazoline then gave the desired oxazole (187) in 58% overall yield (Scheme 50).



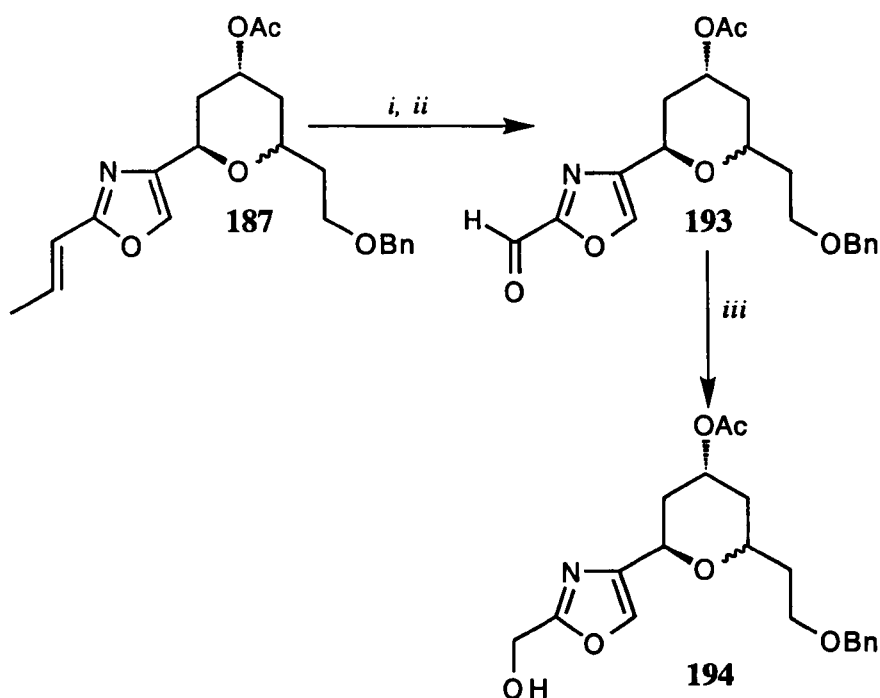
Reagents: i, Dess-Martin periodinane, CH₂Cl₂; *ii*, BrCl₂CCl₂Br, PPh₃, 2,6-di-*tert*-butylpyridine, CH₂Cl₂; *iii*, DBU, CH₃CN, 58%.

Scheme 50

2.1.5 Coupling Protocol

With the oxazole-pyran fragment (187) in hand, our next task was to cleave the crotonyl residue in 187 to the corresponding aldehyde (193) in readiness for further functionalisation. It is known that oxazole rings are sensitive to ozone,⁹² so we chose to dihydroxylate the olefin in 187 with catalytic osmium tetroxide and NMO and then subject the crude 1,2-diol to oxidative cleavage with sodium periodate. This procedure afforded the corresponding aldehyde (193) in 88% overall yield. Subsequent reduction of the aldehyde with sodium borohydride then gave the primary alcohol (194) in 89% yield (Scheme 51).

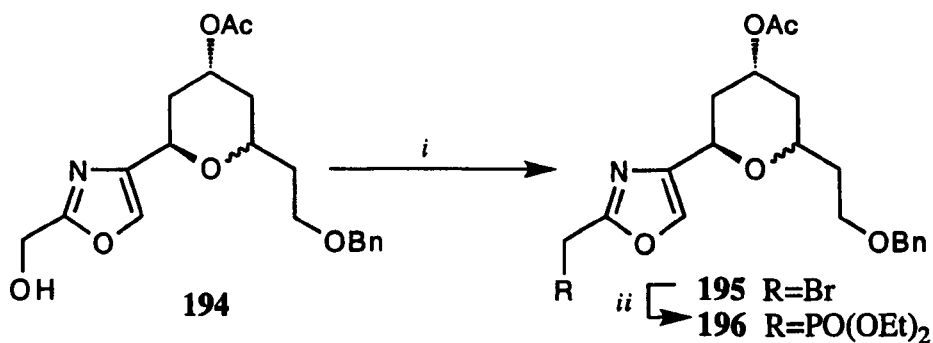
We anticipated that conversion of the primary alcohol group in 194 into a phosphonate would provide a useful precursor for a Wadsworth-Emmons reaction with a suitable aldehyde. Thus, the alcohol (194) was converted into the corresponding bromide



Reagents: i, NMO, OsO₄ (cat.), acetone, H₂O; *ii*, NaIO₄, SiO₂, CH₂Cl₂, 88%; *iii*, NaBH₄, MeOH, 89%.

Scheme 51

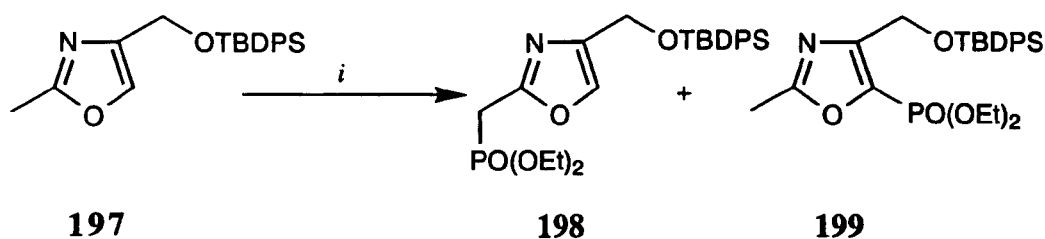
(195) in 80% yield with carbon tetrabromide and triphenylphosphine. Conversion of the bromide (195) into the phosphonate (196) then proceeded quantitatively *via* an Arbusov reaction with triethylphosphite (Scheme 52).



Reagents: i, CBr₄, PPh₃, CH₂Cl₂, 80%; *ii*, P(OEt)₃, toluene, Δ, 100%.

Scheme 52

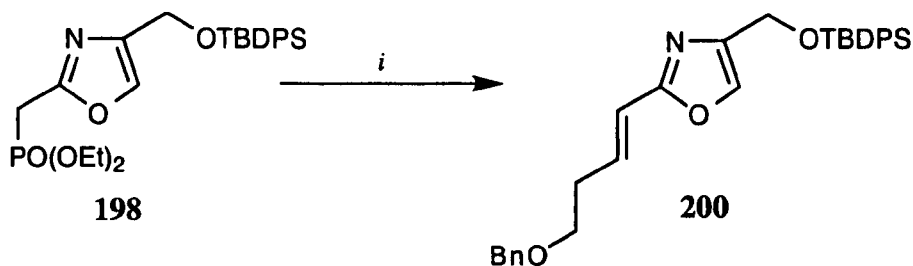
Having prepared the desired oxazole-pyran fragment bearing a phosphonate at the 2-methyl position of the oxazole, we then considered possible conditions for the Wadsworth-Emmons coupling reaction. We chose to model the system with a simple oxazole-phosphonate (**198**). This compound (**198**) could be accessed *via* deprotonation of 2-methyl-4-(*tert*-butyldimethylsilyloxymethyl)oxazole (**197**) with *n*-butyl lithium and quenching with diethyl chlorophosphate (**Scheme 53**). This led to only modest yields of the desired phosphonate (**198**), but sufficient material for our model studies. The oxazole phosphonate (**199**) resulting from deprotonation at the 5-position of the oxazole was also observed in a similar yield. Using a more bulky base (LiHMDS) or changing the protecting group at the 4-position led to no significant increase in the yield or ratio of the two phosphonates. These regioisomers were separated by careful flash chromatography.



Reagents: *i*, *n*-BuLi, diethyl chlorophosphate, THF, 25%.

Scheme 53

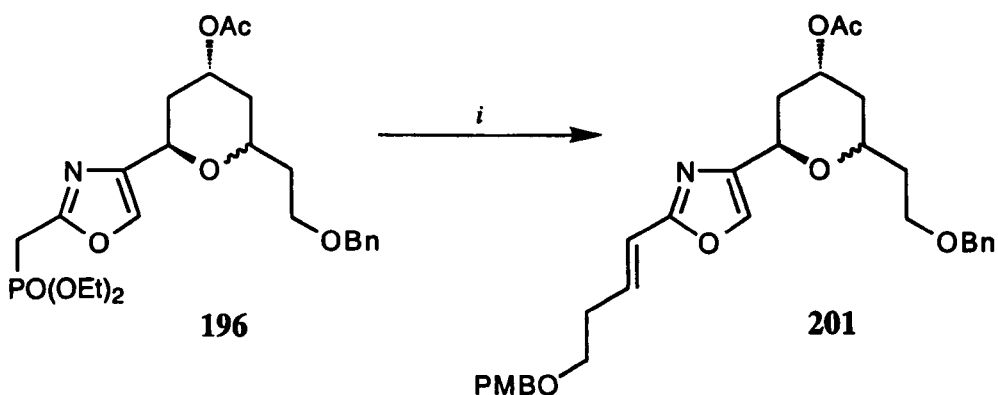
We decided that with phosphonates of type **198**, which mimic β -keto phosphonates, the Wadsworth-Emmons reaction could be carried out under the mild Masamune-Roush conditions.¹¹² Thus, treatment of the phosphonate (**198**) with DBU, lithium chloride and a simple aldehyde, in this case 3-benzyloxy-propionaldehyde, in acetonitrile at room temperature gave a very satisfactory 74% yield of the desired olefin (**200**) as a 10:1 mixture of *trans*:*cis* isomers which could be separated by flash column chromatography (**Scheme 54**).



Reagents: *i*, LiCl, DBU, 3-benzyloxy-propionaldehyde, CH₃CN, 74%.

Scheme 54

Gratified by this result we then decided to examine whether the functionality contained in our oxazole-pyran fragment (**196**) would tolerate these reaction conditions. Again we chose to use a simple aldehyde, 3-(*p*-methoxybenzyloxy)-propionaldehyde and under Masamune-Roush conditions¹¹² we were pleased to obtain a 70% yield of the desired olefin (**201**) in exclusively the *trans* geometry ($^3J_{\text{trans}} = 16.1$ Hz) (**Scheme 55**). Thus, we have shown the utility of this approach for the formation of the C-19-C-20 olefin with good selectivity and we hope we can employ this strategy in future approaches.



Reagents: *i*, LiCl, DBU, 3-(*p*-methoxybenzyloxy)-propionaldehyde, CH₃CN, 70%.

Scheme 55

2.1.6 Stereochemistry Determination

Throughout the period of this research we believed we had the desired 2,6-*cis*-tetrahydropyran, by virtue of an *endo* selective hetero Diels-Alder reaction, as demonstrated by our model studies. We still thought it necessary, however, to unambiguously determine the relative configuration of the pyran before coupling to any other key fragments. This proved to be very difficult initially, due to the lack of a suitably crystalline derivative for X-ray analysis. Also, by the complexity of the ^1H NMR spectra as a result of the rotameric nature of these compounds, and the high number of proton signals adjacent to a hetero atom, giving a congested region in the area of interest, making any irradiation studies difficult.

Throughout the series of compounds from the initial cycloadduct (**150**) to the oxazole phosphonate pyran (**196**), only the aldehyde (**193**) had the three protons at the C-2, C-4, C-6 positions of the tetrahydropyran sufficiently separable for NOE analysis.

Initial NOE experiments were encouraging, showing only one enhancement between two protons as expected. It was not until after careful examination of the COSY spectrum and reassignment of the protons at the C-2 and C-4 positions (the transformation from the crotonyl group to the aldehyde causes the C-2 proton to shift further downfield than the C-4 proton), that we realised we actually had a *trans*-tetrahydropyran! (**Figure 2**)

We decided at this time, for final clarification, to synthesise an oxazole-pyran fragment which we knew to be *cis*, and elaborate that to a common intermediate with the hetero Diels-Alder route from Garner aldehyde, for comparison by NMR. We had previously shown that oxazole aldehydes would participate in a hetero Diels-Alder reaction to give *cis*-tetrahydropyrans. Thus we decided to synthesise the oxazole aldehyde (**207**). The

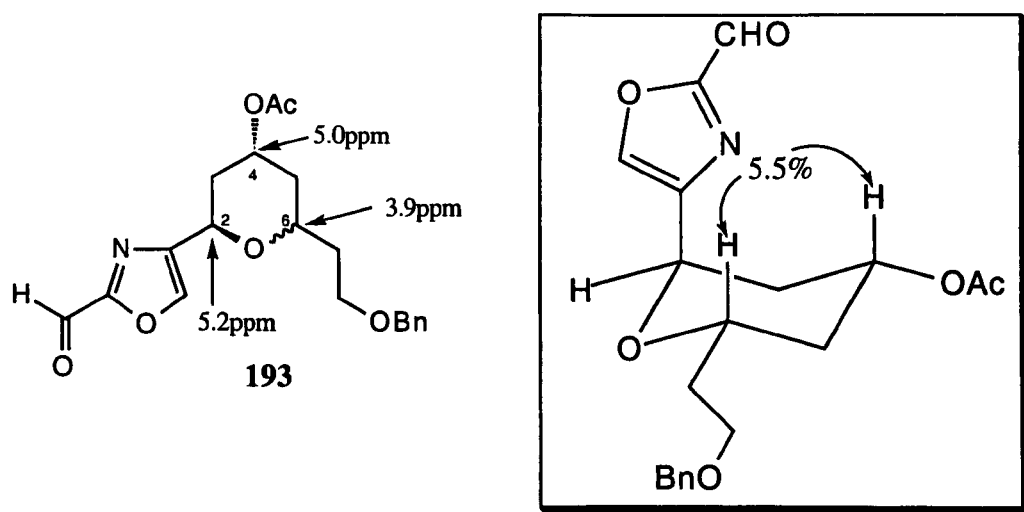
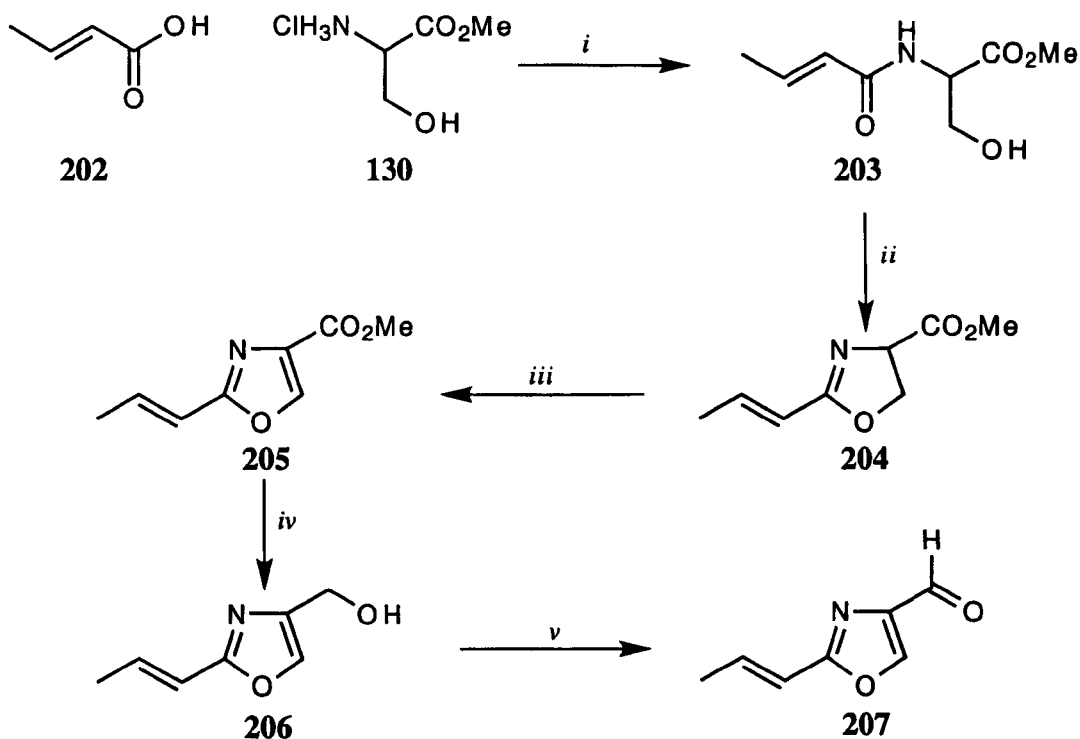


Figure 2: NOE analysis of the oxazole aldehyde (**193**).

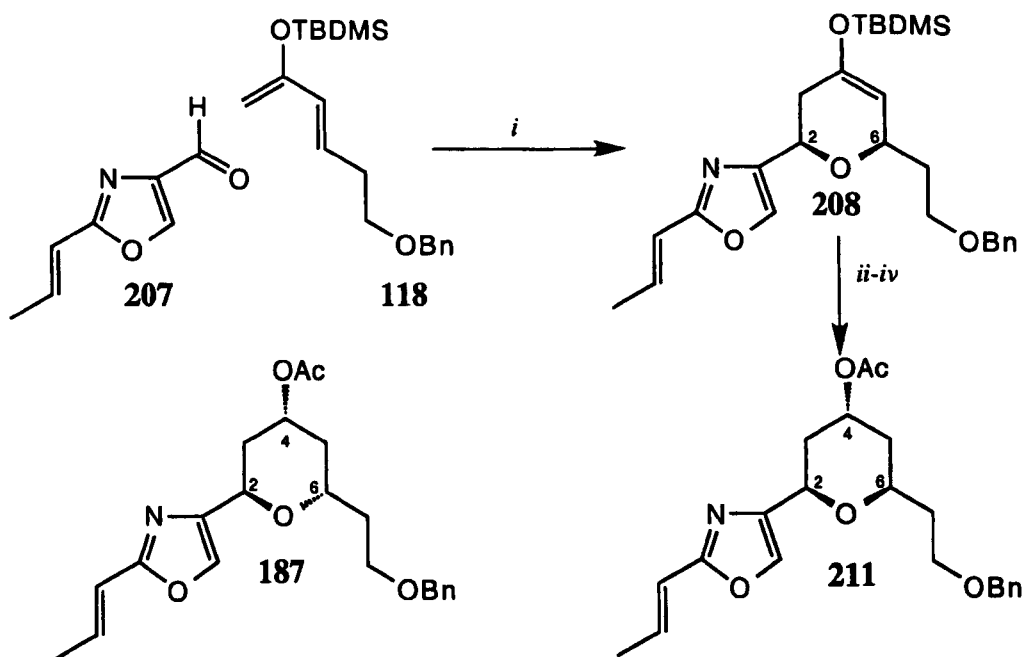
amide (**203**) was achieved under standard amide forming conditions, and converted into the oxazoline (**204**) by a DAST mediated cyclisation. Using the conditions of Williams the oxazole (**205**) was achieved in an excellent 94% yield. Conversion to the aldehyde (**207**) was effected by a DIBAL-H reduction to the alcohol (**206**), followed by oxidation with manganese dioxide (**Scheme 56**).

The dihydropyran (**208**) was then obtained *via* a hetero Diels-Alder reaction between the aldehyde (**207**) and the diene (**118**), in a modest 54% yield as a single diastereomer. The dihydropyran (**208**) was shown to be *cis* by an NOE enhancement of 13% between the C-2 and the C-6 protons. Desilylation with TBAF gave the ketone in 84% yield, which was reduced stereoselectively with L-selectride[®] to give the axial alcohol in 82% yield. Again, NOE data indicated the alcohol to be axial. Acetylation under standard conditions finally gave the acetate (**211**) in quantitative yield (**Scheme 57**).



Reagents: i, EDC, HOBT, Et₃N, THF, 80%; *ii*, DAST, CH₂Cl₂, 77%; *iii*, DBU, BrCCl₃, CH₂Cl₂, 94%; *iv*, DIBAL-H, CH₂Cl₂, 67%; *v*, MnO₂, CH₂Cl₂, 80%.

Scheme 56



Reagents: i, BF₃·Et₂O, Et₂O, 54%; *ii*, TBAF, THF, 84%; *iii*, L-Selectride™, THF, 82%; *iv*, Ac₂O, Et₃N, DMAP (cat.), CH₂Cl₂, 100%.

Scheme 57

By comparison of the ^1H NMR data of **187** and **211**, we observed a significant difference in chemical shifts, giving conclusive proof that **187** did indeed possess the incorrect stereochemistry for incorporation into the phorboxazole macrolide (**Table 2**).

	^1H CHEMICAL SHIFT/PPM		
PROTON	211	187	Δ
C-2	4.7	5.1	-0.4
C-4	5.3	5.1	0.2
C-6	4.0	3.9	0.1

Table 2

We believe the explanation for this disappointing *exo*-selectivity comes from the bulky nature of the BOC group of Garner aldehyde, which prevents the diene approaching in an *endo* manner, due to its steric requirements. Thus, an *exo*-approach is favoured and the *trans*-tetrahydropyran predominates (**Figure 3**).

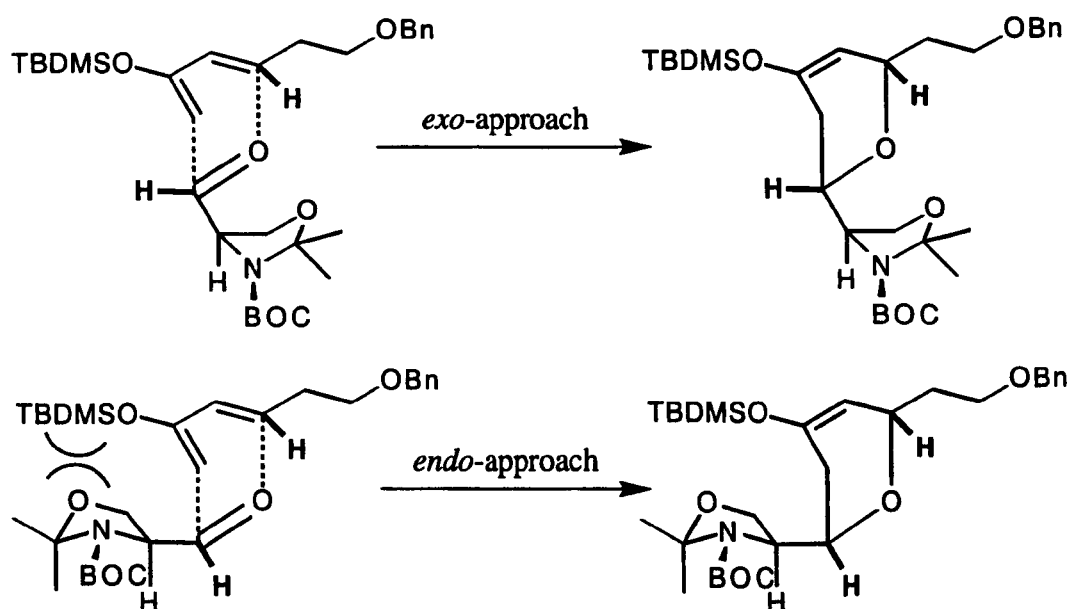
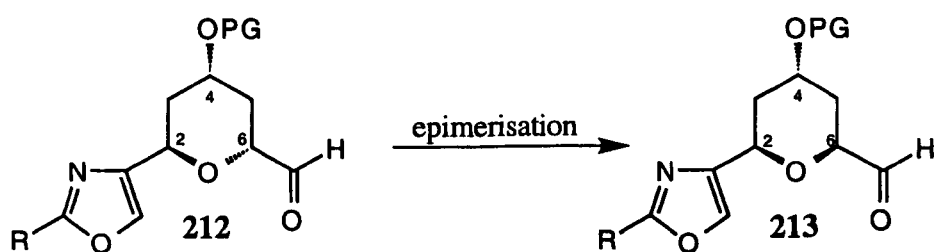


Figure 3

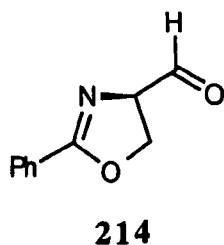
2.1.7 Conclusions

Although the outcome of the hetero Diels-Alder reaction between the diene (**118**) and the aldehyde (**145**) gave the undesired *trans*-product (**150**), there still remains much synthetic scope for this approach. Deamination could provide a facile entry towards *trans*-tetrahydropyrans of polypropionate origin. The possibility also exists for epimerising the *trans*-product (**212**) to the more thermodynamically favoured *cis*-product (**213**) if a one carbon shorter diene fragment was used, which could be elaborated to an aldehyde terminus (Scheme 58).



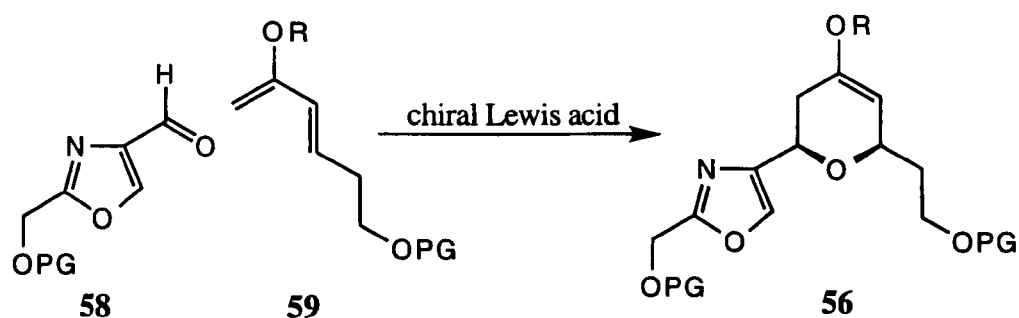
Scheme 58

Another approach would be to use the known oxazoline aldehyde (**214**).¹¹³ We anticipate that this compound is not as sterically demanding as Garner aldehyde, and so may participate in an *endo*-selective hetero Diels-Alder reaction to give the desired *cis*-product. The oxazoline can be cleaved subsequently to the hydroxy amide, for elaboration to the oxazole.



We have demonstrated the effective use of the hetero Diels-Alder reaction with oxazole aldehydes to give *cis*-tetrahydropyrans, albeit with a racemic system. The facile entry to the desired oxazole-pyran system through this route has since prompted us to examine

the use of chiral Lewis acids with this system, giving rise to products with high levels of enantiomeric excess (**Scheme 59**). This research is currently being investigated by colleagues in Nottingham.

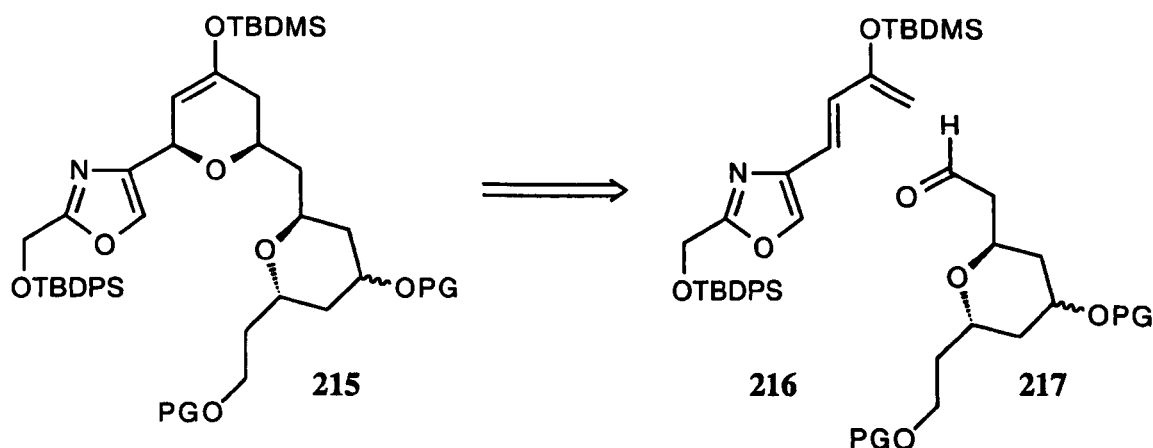


Scheme 59

2.2 Synthetic Approaches Towards *trans*-Tetrahydropyrans

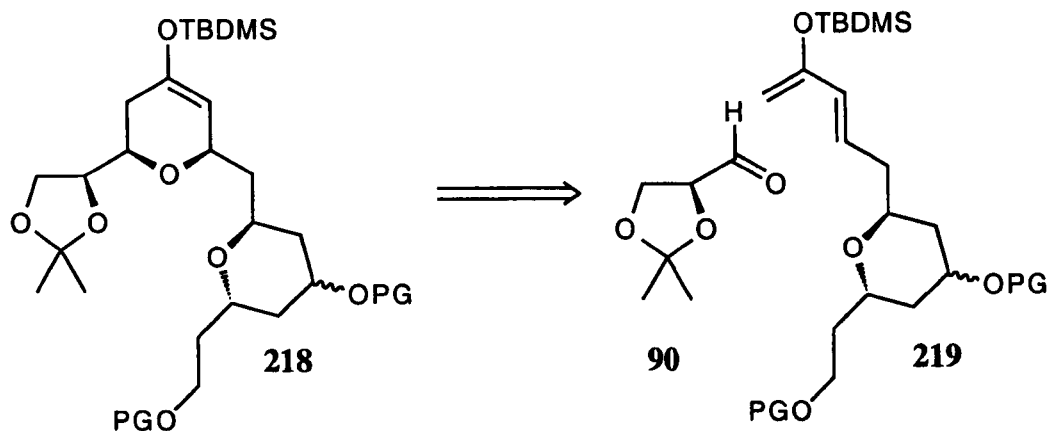
2.2.1 Retrosynthetic Analysis

During the course of our hetero Diels-Alder studies we decided that we would probably require a more convergent strategy towards the oxazole *bis*-pyran unit (**215**). We decided on the possibility of starting with the *trans*-pyran (**217**) and elaborating it towards the oxazole through the *cis*-pyran. Ideally we would have liked to make use of the hetero Diels-Alder chemistry we were currently developing for the *cis*-pyran. We envisaged that the stereochemical outcome of any hetero Diels-Alder reaction may be controlled by the existing chirality of the *trans*-tetrahydropyran aldehyde (**217**) (**Scheme 60**).



Scheme 60

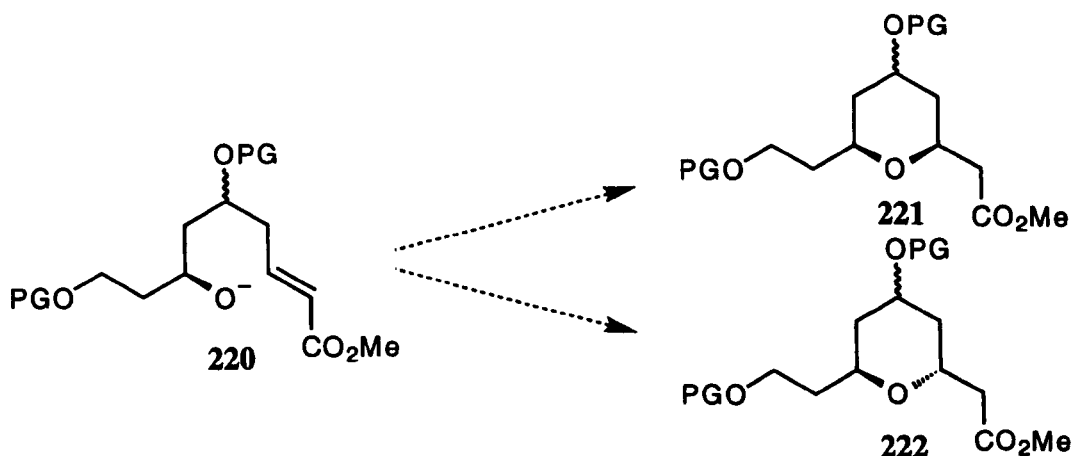
Alternatively, if problems were encountered in the stereoselective formation of the *cis*-pyran (**215**), we could extend the pyran aldehyde (**217**) to the diene (**219**) and use this as the diene in a hetero Diels-Alder reaction with (*S*)-glyceraldehyde acetonide (**90**), which is known to participate in a hetero Diels-Alder reaction with dienes of this type (**Scheme 61**).^{73b}



Scheme 61

2.2.2 Intramolecular Michael Cyclisation - Literature Precedent

We initially decided to try and elaborate the *trans*-tetrahydropyran (**222**). It was our intention to investigate whether we could obtain *cis*- or *trans*-tetrahydropyrans selectively by the intramolecular cyclisation of an alkoxy nucleophile onto a Michael acceptor (Scheme 62).

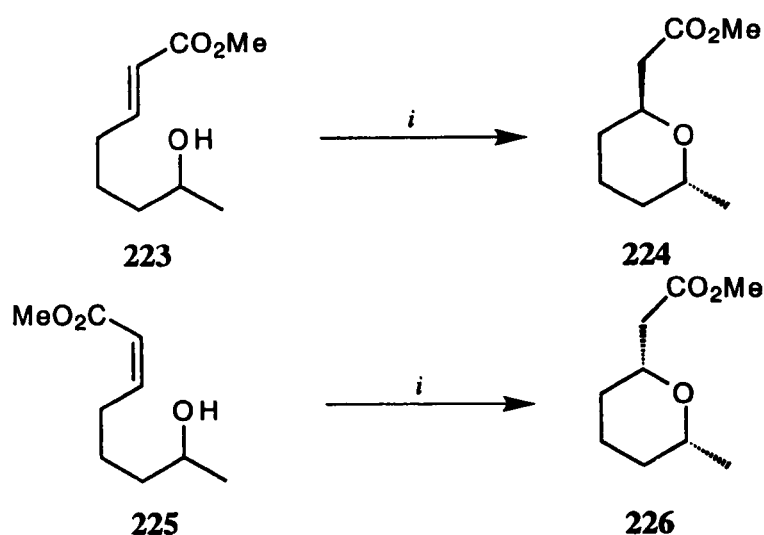


Scheme 62

Recently, two examples of this approach have appeared in the literature leading to 2,6-disubstituted tetrahydropyrans.^{114,115} However, neither have dealt with a system incorporating a substituent at the 4-position of the tetrahydropyran. We were interested

in determining whether the presence of this additional chiral centre would have any effect on the Michael cyclisation, and whether it could help influence a *trans*-geometry.

Banwell *et al* have shown that double bond geometry may be the main control element for the formation of tetrahydropyrans by this route.¹¹⁴ Banwell's research group was able to selectively synthesise both *trans*- (**224**) and *cis*-tetrahydropyrans (**226**) by cyclisation onto a (*E*)-acrylate (**223**) or a (*Z*)-acrylate (**225**) respectively (Scheme 63). Under these conditions (NaH, THF, -78°C - RT), equilibration of the *trans*-isomer (**224**) to the more thermodynamically stable *cis*-isomer (**226**) was not achieved, indicating to us that this approach may well be viable for the synthesis of our desired *trans*-tetrahydropyran.

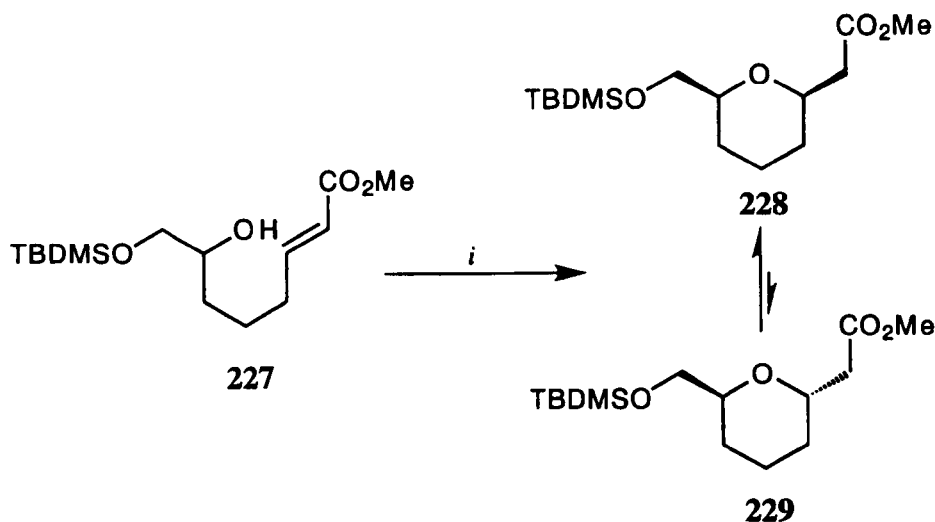


Reagents: *i*, NaH, THF.

Scheme 63

However, in contrast to Banwell's results, Edmunds *et al* have shown that cyclisation of an alkoxide on to an (*E*)-acrylate gives rise to a 1:1 mixture of *cis:trans* tetrahydropyrans very rapidly.¹¹⁵ This mixture can then be equilibrated to the more thermodynamically stable *cis*-isomer (**228**) by prolonged exposure to the reaction conditions at room temperature (Scheme 64). These contrasting results may simply be due to the different substrates used for each study, so we decided to pursue our own

approach towards forming the *trans*-tetrahydropyran bearing the extra functionality required for incorporation to the phorboxazoles.



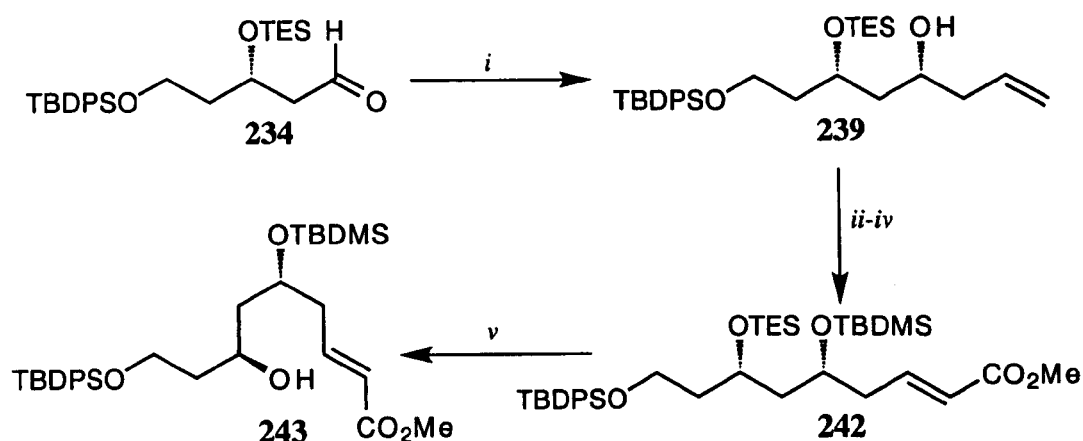
Reagents: *i*, NaH, THF, 93%.

Scheme 64

2.2.3 Intramolecular Michael Cyclisation - Synthetic Studies

We anticipated securing the desired Michael precursor, enantiomerically pure, by employing two successive allylboration following the Brown protocol.¹¹⁶ Thus, 3-buten-1-ol (120) was protected as the *tert*-butyldiphenylsilyl ether (230) and then cleaved to the corresponding aldehyde (231) with ozone. The chiral allyl boron reagent (238) was prepared according to the literature procedure described by Brown *et al.*^{116b} This reagent has been shown to give enantiomeric excesses significantly higher than those reported with previously explored reagents. Hydroboration of (+)-2-carene (235) with borane dimethylsulfide complex gave the crystalline *bis*(2-*isocaranyl*)borane (236), which was readily methanolysed. Treatment of the methoxy derivative (237) with allylmagnesium bromide then led to the desired reagent (238) in good yield. Addition of a solution of 3-(*tert*-butyl-diphenyl-silanyloxy)-propionaldehyde (231) to the chiral allylborane (238) gave, after oxidative workup, a 70% yield of the homoallylic alcohol (232). The enantiomeric excess of the alcohol (232) was

unsaturated ester (**242**) in an excellent 95% yield as a single geometric isomer. A small amount of the corresponding (*Z*)-olefin was also synthesised by employing Still's modification of the Wittig reaction.⁶⁰ Finally, selective deprotection of the triethylsilyl ether in **242** was achieved in 81% yield (based on recovered starting material) with trifluoroacetic acid in aqueous THF to give the desired Michael precursor (**243**). This selective deprotection had to be monitored extensively by TLC to prevent cleavage of the TBDMS ether, and often the reaction was stopped prior to completion in order to prevent diol formation (Scheme 66).

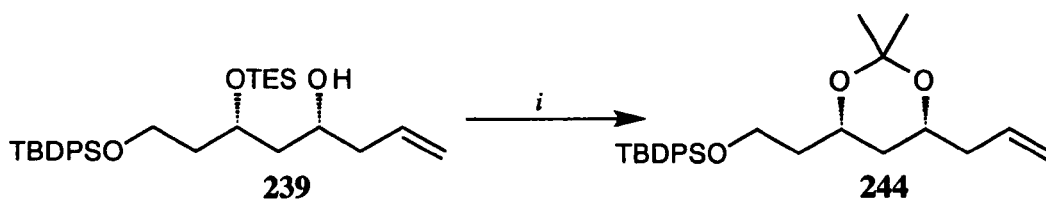


Reagents: i, a) (+)-β-Allyl(Ipc)₂B, Et₂O; b) H₂O₂, NaOH, 70%; ii, TBDMS-OTf, Et₃N, CH₂Cl₂, 80%; iii, a) O₃, NaHCO₃, CH₂Cl₂; b) PPh₃, 89%; iv, Ph₃PCHCO₂Me, CH₂Cl₂, 95%; v, TFA, THF, H₂O, 81%.

Scheme 66

The configuration of the new stereogenic centre of the alcohol (**239**) derived from the allylboration reaction was confirmed as *syn* by analysis of the ¹³C chemical shifts of the derived acetonide (**244**), as described by Rychnovsky¹¹⁸ and Evans.¹¹⁹ Thus, the homoallylic alcohol (**239**) was converted into the acetonide (**244**) in one pot by treatment with PTSA in 2,2-dimethoxypropane in 76% yield. The ¹³C chemical shifts of the acetonide methyl groups in **244** are in accord with a chair conformation giving rise to a large difference in chemical shift between axial and equatorial methyl groups indicating the desired *syn* configuration. Acetonides from *anti* diols give rise to a twist

boat conformation, placing the methyl groups in a similar chemical environment and thus the ^{13}C chemical shifts of the methyl groups would have similar values (**Scheme 67, Figure 4**).



Reagents: i, PTSA, 2,2-DMP, 76%.

Scheme 67

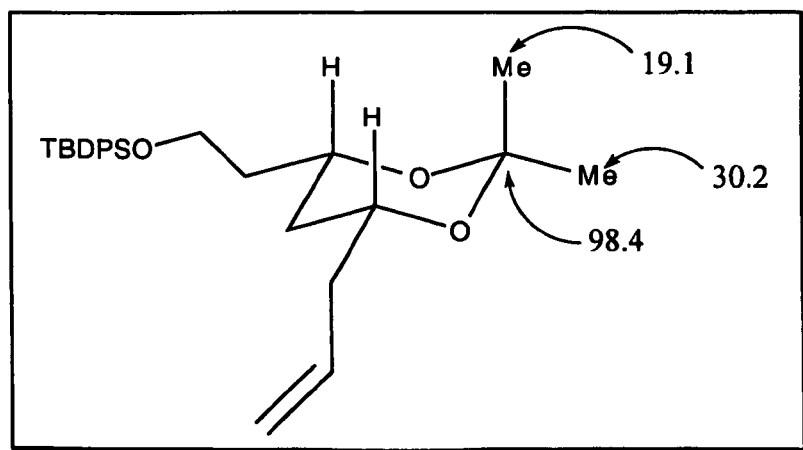
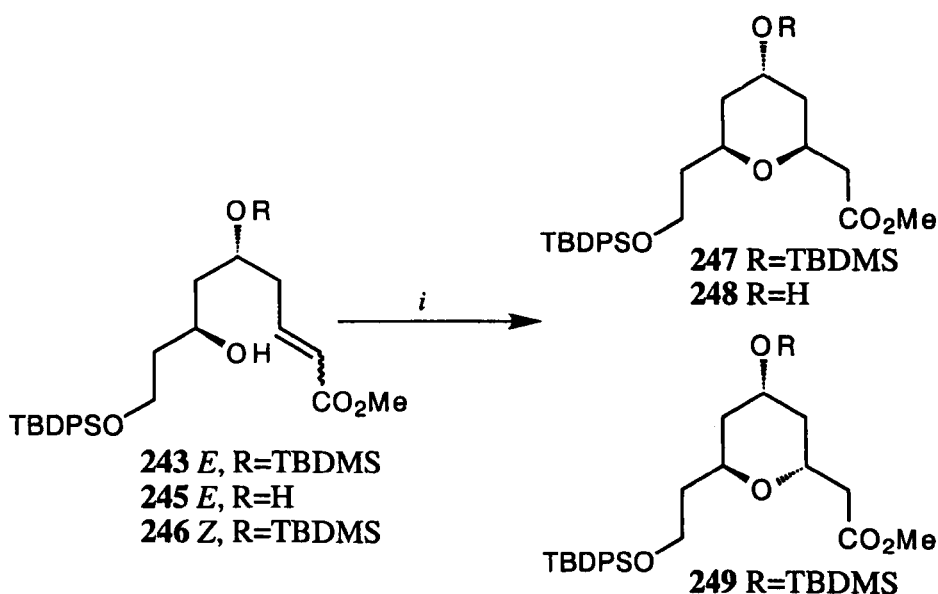


Figure 4: ^{13}C chemical shifts of the acetonide (**244**) illustrating a *syn* configuration.

The *syn* arrangement was carefully chosen as we thought that if an *anti* arrangement was used then one product of the Michael reaction would have a quasi-equatorial arrangement of substituents. We believed the thermodynamic preference of having all three substituents equatorial would be much favoured and predominate. By having a *syn* arrangement this would force one substituent to be in an axial position in whichever diastereomer is formed, thus lowering the difference in energy of the two cyclisation products. Hopefully this approach would create a more favourable chance of obtaining the *cis*- or *trans*-tetrahydropyran selectively. Furthermore, we deemed it necessary for the substituent at the C-4 position to be at the alcohol oxidation state. We believed that if this was to be converted into the *exo* methylene group, then it may undergo

isomerisation into the ring, in conjugation with the unsaturated ester under the reaction conditions. Also a ketone would not be suitable at this position as it may undergo a retro-aldol transformation under the reaction conditions.

With the desired Michael precursors (**243**, **245**, **246**) in hand we attempted the cyclisation to the tetrahydropyran (**Scheme 68**) under a variety of conditions, with the main emphasis being on temperature and base, as summarised in **table 3**.

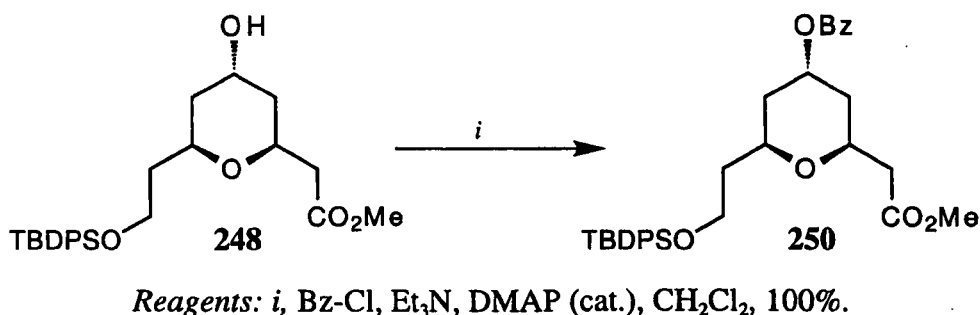


Scheme 68

Entry	Precursor	Conditions, <i>i</i>	Yield	<i>cis:trans</i>
1	243	NaH, THF, -78°C-0°C	100%	1.4:1
2	243	NaH, THF, RT	70%	1:1
3	243	KtBuO, THF, -78°C	90%	1.5:1
4	243	KtBuO, THF, RT	25%	<i>cis</i> only
5	243	LiHMDS, THF, -78°C	82%	8:1
6	245	NaH, THF, RT	50%	<i>cis</i> only
7	246	NaH, THF, RT	90%	7:1

Table 3

Our determination of the *cis:trans* ratios was based on integration of the proton signals *alpha* to the ester. The protons *alpha* to the ester of the *trans*-pyran resonate further downfield (2.76 - 2.53ppm) than those of the *cis*-pyran (2.53 - 2.32ppm) based on literature comparison.¹¹⁴ To verify that this was indeed the case, the product from entry 6 (**248**) was benzoylated in quantitative yield (**Scheme 69**) and NOE experiments were performed on **250** which showed a strong enhancement of 5.5% between the protons at the C-2 and C-6 positions of the pyran. No enhancement was observed between the proton at C-4 and the protons at the C-2 and C-6 positions indicating the benzoyl group is axially disposed (**Figure 5**).



Scheme 69

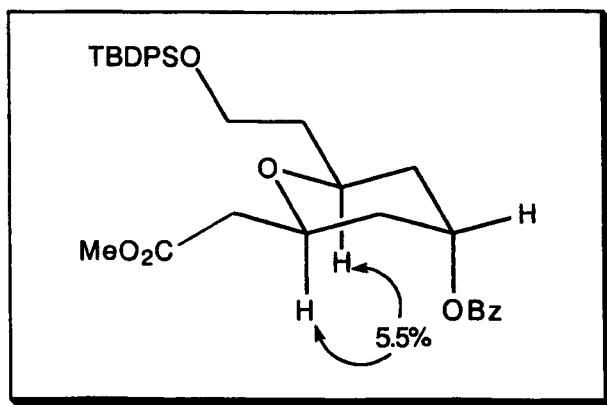


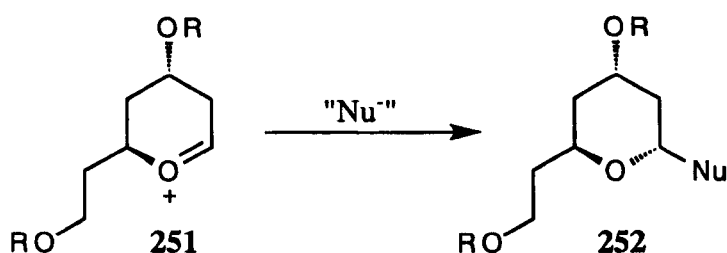
Figure 5: NOE irradiation studies of the pyran (**250**) indicating *cis*-substitution.

Under no circumstances could the desired *trans*-isomer (**249**) be obtained as the major product. It was apparent that the substituent at the C-4 position of the pyran was having some effect on the outcome of the cyclisation. When the diol (**245**) was cyclised a stronger preference for the *cis*-isomer (**248**) resulted, indicating that in this case the *cis*-

isomer is the thermodynamic product with the two largest groups at the C-2 and C-4 positions occupying equatorial orientations. These observations follow the results of Banwell *et al.*,¹¹⁴ showing that the (*Z*)-olefin (**246**) gives the *cis*-isomer (**247**) with good selectivity.

2.2.4 Allylation Approach

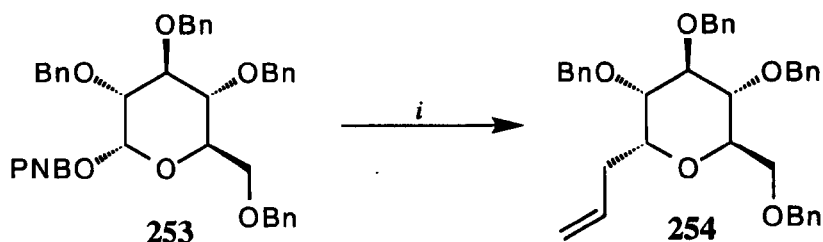
Disappointed by the low levels of selectivity in favour of the *trans*-pyran (**249**) from the Michael cyclisation, we turned our attention to an alternative method of forming the desired *trans*-pyran by an allylation approach. We anticipated that we could make use of the two chiral centres in the material that we had prepared previously for the Michael addition study. We hoped that the stereochemical control of the allylation could be realised by nucleophilic addition to a pyran oxonium ion (**251**) (Scheme 70). The oxonium ion should preferentially accept nucleophiles from the α (axial) face due to the anomeric effect from the ring oxygen, giving rise to a *trans*-tetrahydropyran (**252**).



Scheme 70

Indeed, Kishi *et al* have shown the synthetic utility of this reaction by the synthesis of α -C-glycopyranosides required for their synthetic studies towards palytoxin.¹²⁰ Thus, 2,3,4,6-tetrabenzyl- α -(*p*-nitrobenzoyl)glucopyranose (**253**) was reacted with allyl trimethylsilane and boron trifluoride diethyl etherate in acetonitrile at room temperature for three hours to give a 10:1 mixture of allylglycopyrans in 80% yield, in favour of the *trans*-pyran (**254**) (Scheme 71). Several other research groups have also used this strategy with success. Indeed both Nicolaou and Paterson have successfully used this

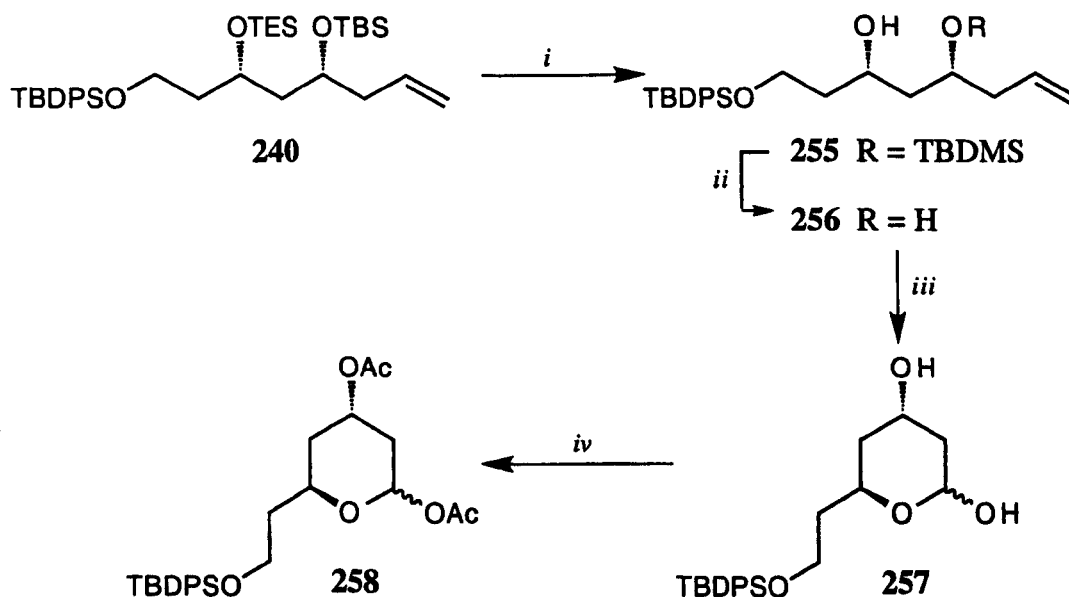
strategy in their independent syntheses of the *trans*-tetrahydropyran present in swinholid A.¹²¹



Reagents: *i*, AllylTMS, BF₃·Et₂O, CH₃CN, 80%.

Scheme 71

Thus, we were able to use the *tris*-silyl ether (**240**) derived from the allylboration sequence as discussed previously. Exposure of **240** to trifluoroacetic acid in wet THF resulted in a mixture of the alcohol (**255**) and the diol (**256**). Further exposure of the alcohol (**255**) to trifluoroacetic acid gave the desired diol (**256**). The diol was then treated with ozone to give, after reductive work up, the *hemi*-acetal (**257**) as a 3:1

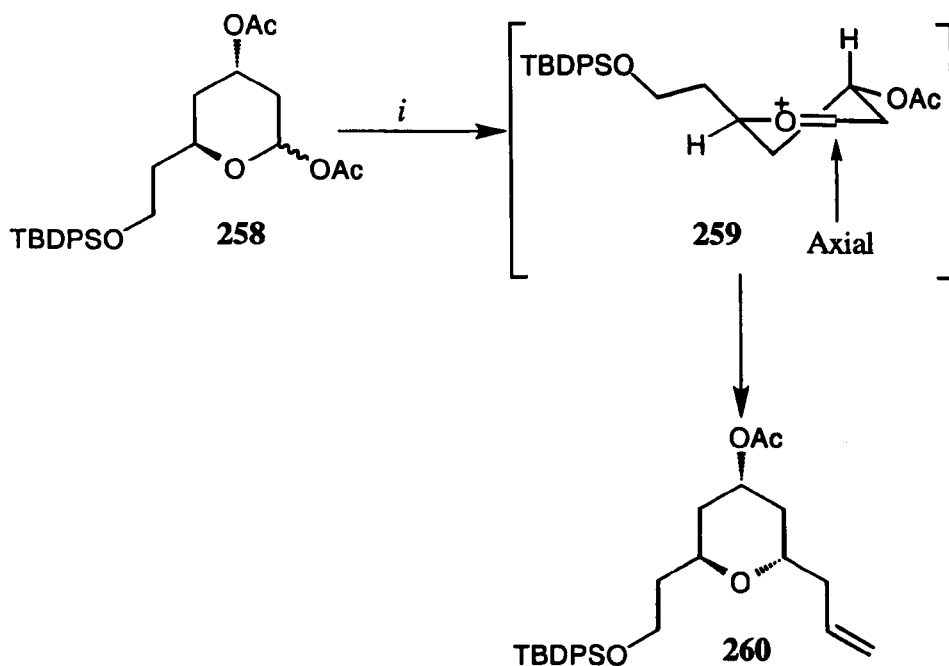


Reagents: *i*, TFA, THF, H₂O, 57% (**255**), 42% (**256**); *ii*, TFA, THF, H₂O, 61%; *iii*,
a) O₃, CH₂Cl₂; *b*) PPh₃, 95%; *iv*, Ac₂O, Et₃N, DMAP (cat.), CH₂Cl₂, 86%.

Scheme 72

mixture of anomers in 95% yield, which were taken through without separation. Acetylation of the diol (**257**) then furnished the *bis*-acetate (**258**), the allylation precursor (**Scheme 72**).

Treatment of the *bis*-acetate (**258**) with allyltrimethylsilane, catalytic TMS-OTf and boron trifluoride diethyl etherate at -78°C led, *via* kinetically controlled axial attack on the oxonium ion (**259**), to the rapid and clean formation of the *trans*-substituted tetrahydropyran (**260**) as a single diastereoisomer in an excellent 94% yield (**Scheme 73**). The use of the strong Lewis acid TMS-OTf as described by Hosomi *et al* allows for the allylation to take place at low temperature, very quickly, and with enhanced levels of stereoselectivity.¹²² The low temperature must be maintained to prevent Lewis acid mediated silyl ether cleavage, which was observed on allowing the solution to warm up to 0°C .



Reagents: i, AllylTMS, BF₃.Et₂O, TMS-OTf, CH₃CN, CH₂Cl₂, 94%.

Scheme 73

The stereochemical outcome of the allylation was proven to be *trans* by the observation of an NOE between the protons at the C-2 and C-4 positions of **260**, indicating that

these two protons are in axial positions. The absence of an NOE from the proton at the C-6 position with either of the protons at the C-2 and C-4 positions, indicates that the C-6 substituent is axially disposed and therefore a *trans* arrangement exists (Figure 6).

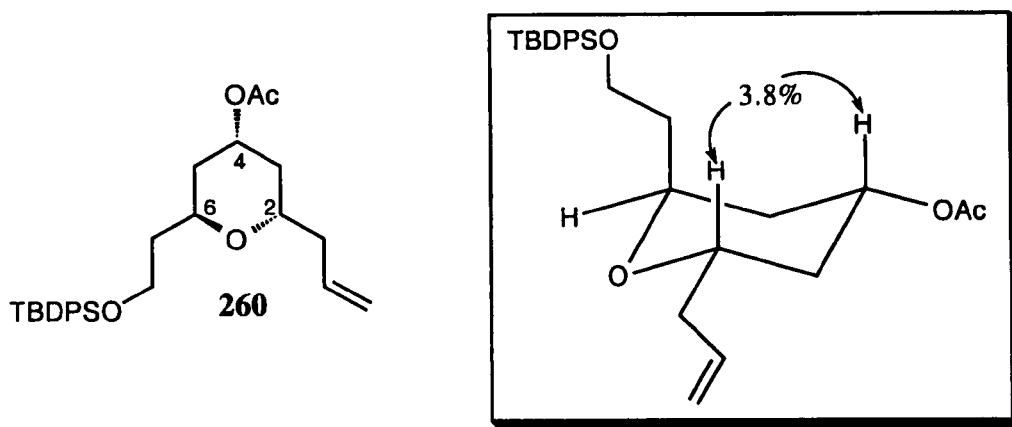


Figure 6: NOE analysis of the *trans*-pyran (260).

2.2.5 Conclusion

Although we were unsuccessful in utilising a Michael cyclisation to form the *trans*-tetrahydropyran, we have demonstrated the efficiency of *cis*-tetrahydropyran formation by this approach. This general approach is currently being pursued by my colleague Alleyn Plowright for the formation of the *cis*-tetrahydropyran (55) present within the macrolide.

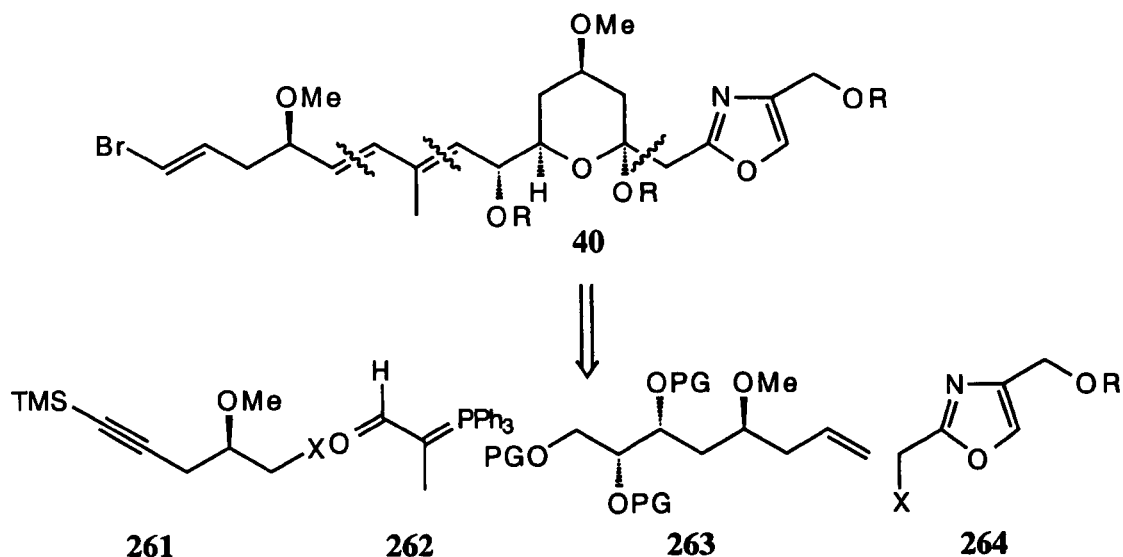
We have also described a highly efficient and stereoselective route towards the *trans*-tetrahydropyran (260) which is suitably functionalised for further elaboration towards the oxazole *bis*-pyran unit (215). This material could be used, as described earlier, in a hetero Diels-Alder reaction to form the *cis*-pyran (Scheme 60), or just taken as a model study showing the utility of the allylation protocol for the formation of *trans*-tetrahydropyrans.

2.3 Synthetic Studies Towards the Side Chain

2.3.1 Retrosynthetic Analysis

The side chain unit (**40**) of phorboxazole A provides a significant challenge to the synthetic organic chemist. The vast array of functionality present in this unit leaves the way open for many possible synthetic approaches. Disconnection of phorboxazole A across the C-27-C-28 double bond (**Scheme 3**) gives the target fragment (**40**), incorporating a 2,4-disubstituted oxazole, a *hemi*-acetal pyran, an (*E,E*)-1,3-diene unit and a (*E*)-vinyl bromide terminus. The fragment also bears eight stereochemical elements in five stereogenic centres and three olefin units. At the outset of my project we were unsure whether to include the oxazole unit, or omit it for inclusion at a later stage. Proceeding without the oxazole gives us extra flexibility when we attempt coupling protocols in assembling the various fragments. During our studies towards the side chain (**40**) we have pursued several approaches including oxazole formation at an early stage and a complementary approach to the side chain in the absence of the oxazole.

Our general retrosynthetic analysis was focused towards implementing two successive olefination reactions to introduce the (*E,E*)-1,3-diene unit in **40** in a highly selective manner. Unravelling the *hemi*-acetal portion in **40** gives the polyol fragment (**263**) containing three chiral centres. We gave ourselves the option of installing the oxazole as a single unit by means of a nucleophilic displacement reaction or alternatively allowing the oxazole to be built up in a stepwise manner *via* a hydroxy-amide. We anticipated that a protected acetylene would serve as a suitable precursor to the vinyl bromide unit in **40** at a late stage (**Scheme 74**).



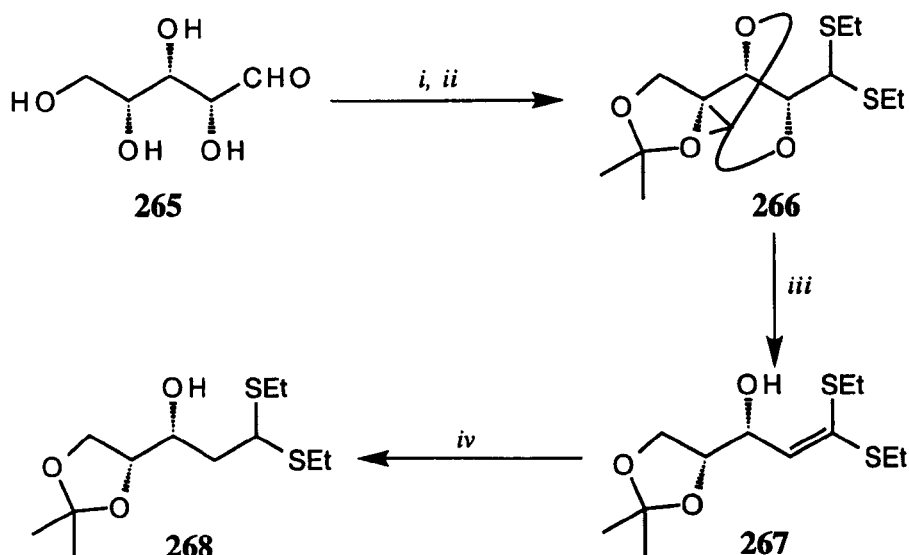
Scheme 74

2.3.2 The Chiral Pool Approach

It was our first concern to establish the necessary methodology for the central *hemi*-acetal pyran precursor (**263**) incorporating the majority of the chirality in the side chain. We anticipated that we could produce the desired material from a chiral pool sugar. Gray *et al* have shown that 2-deoxy sugars can be synthesised in a short sequence of steps from their parent sugars.¹²³ The utility of this route has been demonstrated by White *et al* in their synthesis of constanolactone from the sugar arabinose.¹²⁴ The configuration required for incorporation to the side chain of phorboxazole A necessitates the use of (*D*)-xylose. (*D*)-Xylose (**265**) was converted into the 2-deoxypentose dithioacetal (**268**) in a similar manner to that described by White *et al* for arabinose,¹²⁴ although a few slight modifications were required as the intermediate dithioacetal was not crystalline, and so isolation became slightly more difficult.

Thus, (*D*)-xylose (**265**) was first converted to the dithioacetal which was next protected as the *bis*-acetonide (**266**). Without purification the *bis*-acetonide (**266**) was subjected to a base-promoted elimination to give the dithioketeneacetal (**267**) in an

overall yield of 35% for three steps on a 50g scale. Hydroxyl directed reduction of **267** with lithium aluminium hydride gave the desired deoxy sugar derivative (**268**) in 90% yield (Scheme 75).

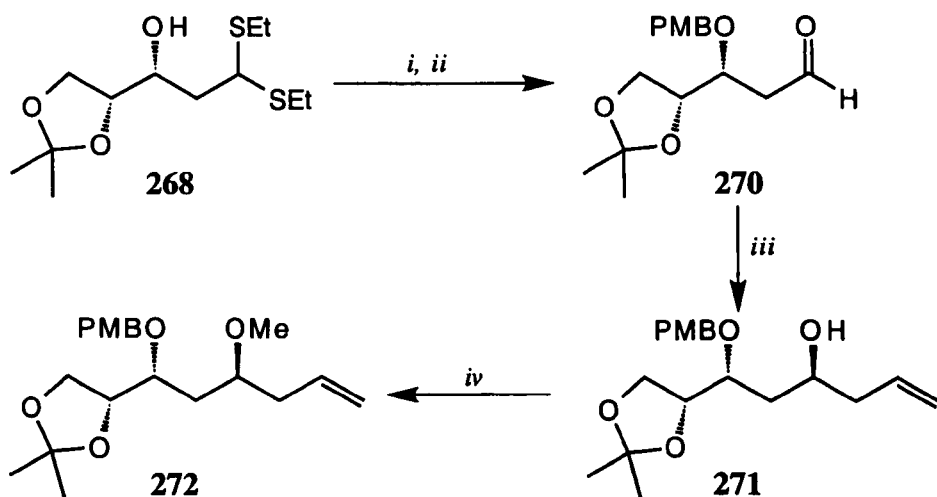


Reagents: i, EtSH, 6M HCl; ii, Me₂CO, H₂SO₄; iii, K^tBuO, DMSO, THF, 35% (3 steps); iv, LiAlH₄, THF, 90%.

Scheme 75

Installation of the third stereogenic centre in **263** to complete the fragment was the next requirement. We believed that an allylation reaction would provide the desired *anti*-geometry under substrate control, whilst also including a functional group for further elaboration. Thus, protection of the alcohol (**268**) as the *p*-methoxybenzyl ether (**269**) was achieved with *p*-methoxybenzyl bromide and potassium *tert*-butoxide in 98% yield. Deprotection of the dithioketal with buffered mercury perchlorate gave the aldehyde (**270**) in 91% yield. We were now in a position to investigate the conditions required for the allylation. Treatment of the aldehyde (**270**) with allyltrimethylstannane and boron trifluoride diethyl etherate gave the alcohol (**271**) as an inseparable 3.5:1 ratio of diastereomers in an excellent 98% yield. We were slightly disappointed by the low levels of stereoselectivity under the substrate controlled conditions and so we turned our attention to a reagent controlled allylation. Treatment of the aldehyde (**270**)

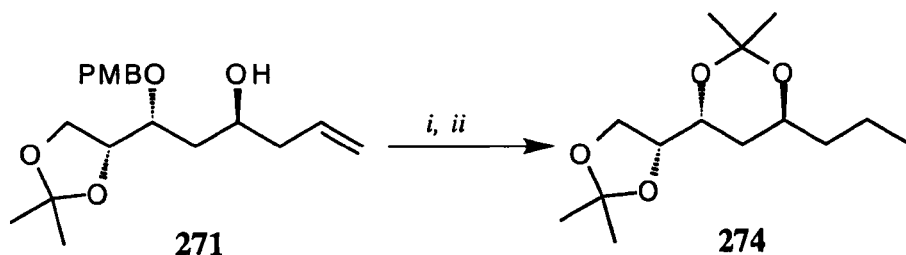
with (-)- β -allyl diisopinocampheylborane^{116a} followed by oxidation with basic hydrogen peroxide solution led to the homoallylic alcohol (**271**) in over 80% yield, with an enhanced stereoselectivity of 8:1. Subsequent methylation under standard conditions gave the desired fragment (**272**) and facilitated isomer separation (**Scheme 76**).



Reagents: *i*, KtBuO , PMB-Br , Bu_4NI , THF, 98%; *ii*, $\text{Hg}(\text{ClO}_4)_2$, CaCO_3 , THF, 91%; *iii*, *a\beta-Allyl(Ipc)₂B, Et_2O ; *b*) H_2O_2 , NaOH , 82%; *iv*, KtBuO , MeI , THF, 98%.*

Scheme 76

The *anti*-configuration of the new stereogenic centre of the alcohol (**271**) derived from the allylboration reaction was confirmed by analysis of the ^{13}C chemical shifts of the derived acetonide, using the method of Rychnovsky¹¹⁸ and Evans.¹¹⁹ Thus, the alcohol (**271**) was converted to the acetonide (**274**) in two steps by hydrogenation of the *p*-methoxybenzyl ether and olefin to give the diol (**273**) followed by acetonide formation under standard conditions in an overall yield of 81%. The ^{13}C chemical shifts of the acetonide methyl groups are in accordance with a twist boat conformation giving rise to very similar chemical shifts of the two methyl groups, indicating the desired *anti* configuration (**Scheme 77**, **Figure 7**).



Reagents: i, Pd/C, H₂, MeOH; ii, PTSA, 2,2-DMP, 81% (2 steps).

Scheme 77

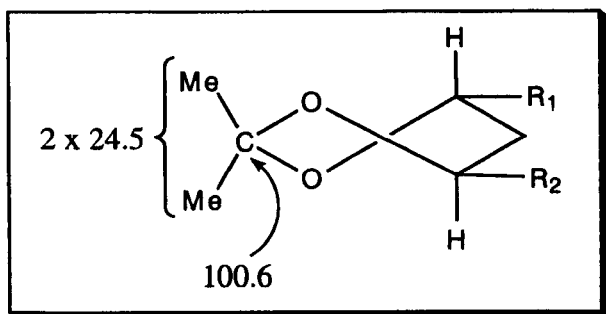
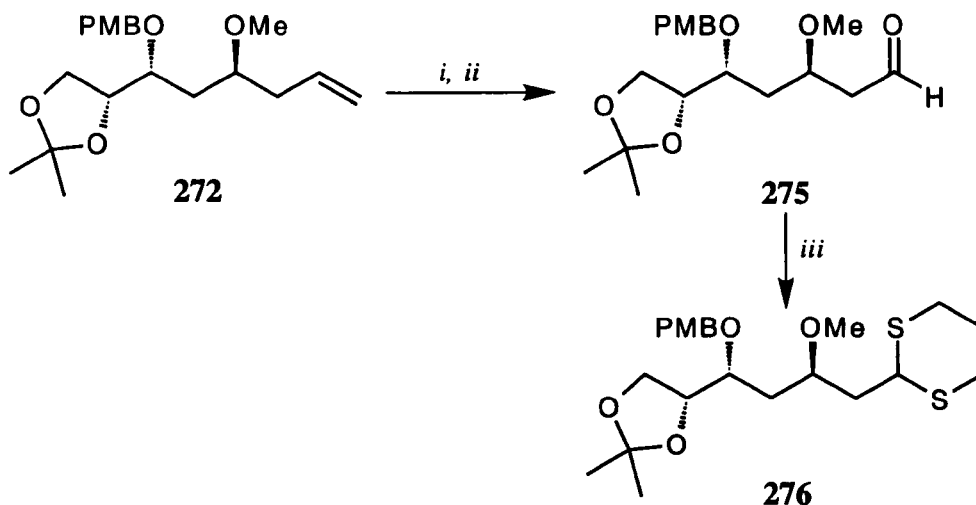


Figure 7: ¹³C chemical shifts of the acetonide (274) indicating an *anti*-configuration.

2.3.3 Dithiane Approach for Oxazole Introduction

It was now our intention to convert the olefin (272) into the corresponding 1,3-dithiane (276) for subsequent coupling to an oxazole. Although the coupling of 1,3-dithianes to electrophiles have been exploited in the total syntheses of many natural products, the general utility of this approach has been problematic. Metallation of a substituted dithiane usually requires the use of a strong base, solvent additive and a myriad of time and temperature regimes. However, in the course of synthetic studies towards rapamycin by Smith *et al* they demonstrated the generality of the *tert*-butyl lithium HMPA / THF protocol for the rapid metallation of highly functionalised 2-alkyl-1,3-dithianes.¹²⁵ We anticipated we could use these conditions within our own system. Thus, dihydroxylation and oxidative cleavage of 272 proceeded uneventfully to give the aldehyde (275) in excellent overall yield. However, formation of the dithiane (276) proved to be very difficult. Under acidic conditions, the acetonide was cleaved giving

rise to a mixture of products. Under milder conditions (ZnI_2 (cat.), $(\text{TMS-SCH}_2)_2\text{CH}_2$),¹²⁶ we were able to obtain the dithiane (**276**) but only in poor yield (Scheme 78).

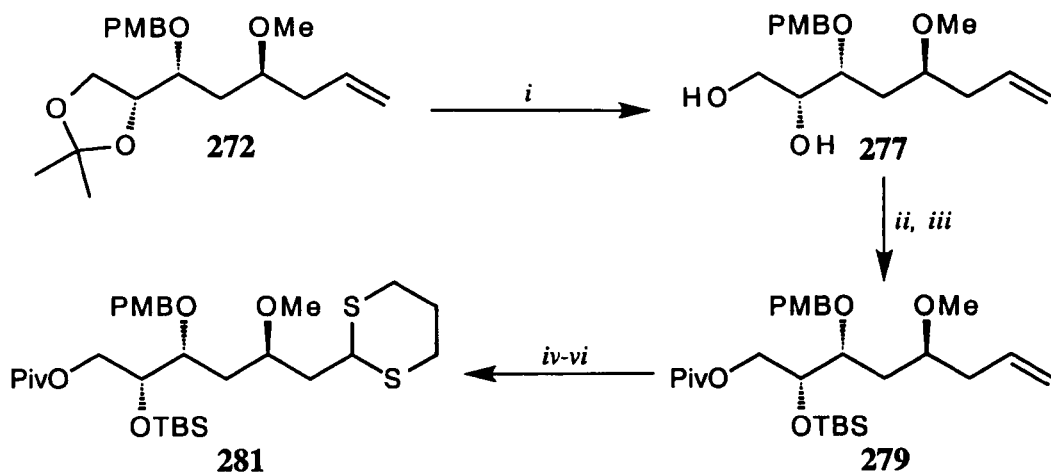


Reagents: *i*, OsO_4 , NMO, Acetone, H_2O ; *ii*, NaIO_4 , SiO_2 , CH_2Cl_2 , 96% (2 steps); *iii*, $(\text{TMS-SCH}_2)_2\text{CH}_2$, ZnI_2 (cat.), Et_2O , 15%.

Scheme 78

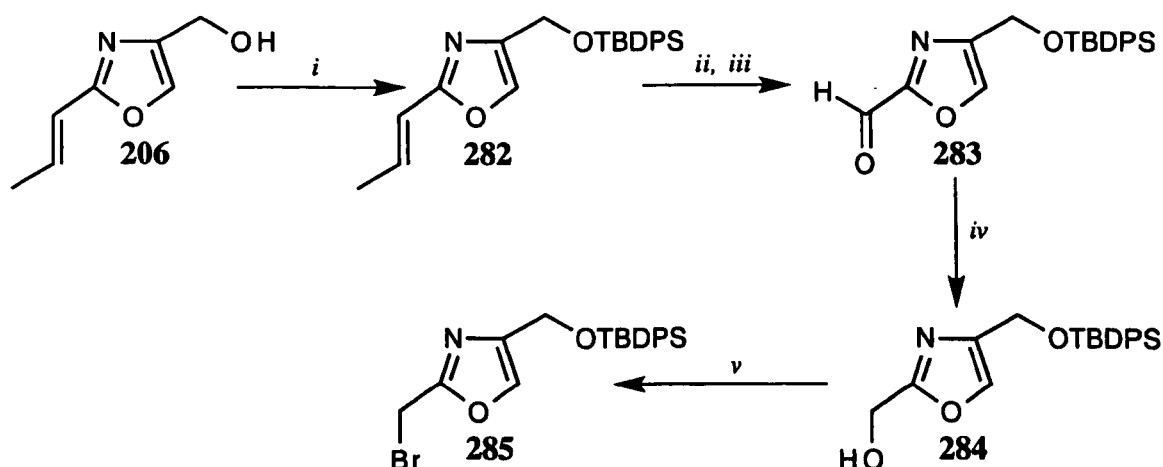
We decided at this stage to adjust our protecting group strategy, prior to olefin formation. Thus, the acetonide in **272** was cleaved with acidic methanol leading to the diol (**277**) in 88% yield. The diol (**277**) was protected sequentially as a pivalate ester on the primary hydroxyl and then as a *tert*-butyldimethylsilyl ether on the secondary hydroxyl, both in good yield. Dihydroxylation and diol cleavage of **279** then gave the aldehyde (**280**) in excellent yield. Dithiane (**281**) formation¹²⁶ from the aldehyde (**280**) was then achieved in an acceptable 65% yield (Scheme 79).

An electrophilic oxazole unit was now required for the key alkylation step. Thus, the oxazole alcohol (**206**) was protected as the *tert*-butyl diphenylsilyl ether (**282**) followed by oxidative cleavage of the olefin to give the aldehyde (**283**). Sodium borohydride reduction of the aldehyde (**283**) led to the alcohol (**284**), which was subsequently converted to the bromide (**285**) in good overall yield (Scheme 80).



Reagents: *i*, CSA, MeOH, 88%; *ii*, Piv-Cl, DMAP (cat.), Py., 92%; *iii*, TBS-OTf, Et₃N, CH₂Cl₂, 100%; *iv*, OsO₄, NMO, Acetone, H₂O; *v*, NaIO₄, SiO₂, CH₂Cl₂, 93% (2 steps); *vi*, (TMS-SCH₂)₂CH₂, ZnI₂ (cat.), Et₂O, 65%.

Scheme 79

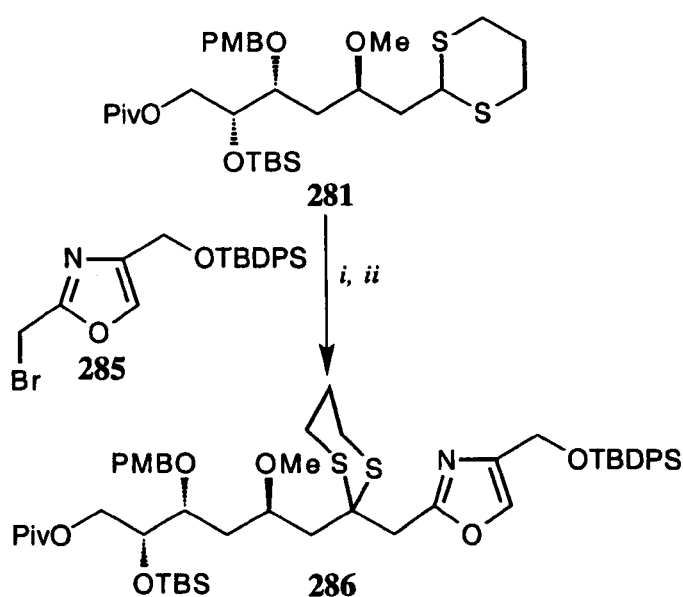


Reagents: *i*, TBDPS-Cl, Et₃N, DMAP (cat.), CH₂Cl₂, 100%; *ii*, OsO₄, NMO, Acetone, H₂O; *iii*, NaIO₄, SiO₂, CH₂Cl₂, 69% (2 steps); *iv*, NaBH₄, MeOH, 100%; *v*, CBr₄, PPh₃, CH₂Cl₂, 75%.

Scheme 80

The key coupling step between the dithiane (281) and the bromide (285), using the Smith protocol,¹²⁵ proved to be exceptionally difficult, especially on a very small scale. Each investigation led to many products and only on one occasion was the desired product (286) obtained, albeit in a mixture of seven other compounds in less than 10%

yield (**Scheme 81**). A major by-product observed was loss of the pivolate ester in **281**. Employment of the corresponding oxazole mesylate as an alternative electrophile also failed to give an increased yield of the desired product (**286**). Several other research groups have also encountered the often capricious nature of highly oxygenated dithiane anions,¹²⁷ for this reason and the instability of both substrates under the reaction conditions we decided not to pursue this approach. We believe the strongly basic conditions may be responsible for oxazole decomposition, as we were unable to recover any of the oxazole.



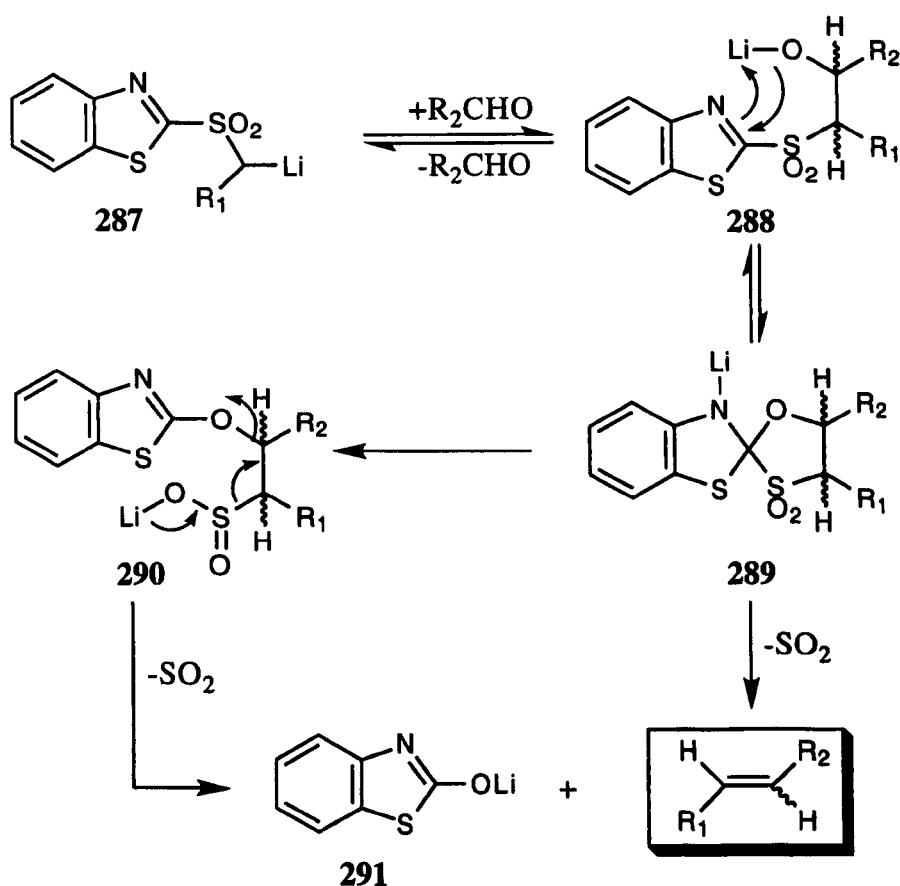
Reagents: i, tBuLi, HMPA, THF; ii, 285, THF.

Scheme 81

2.3.4 Olefination Protocol

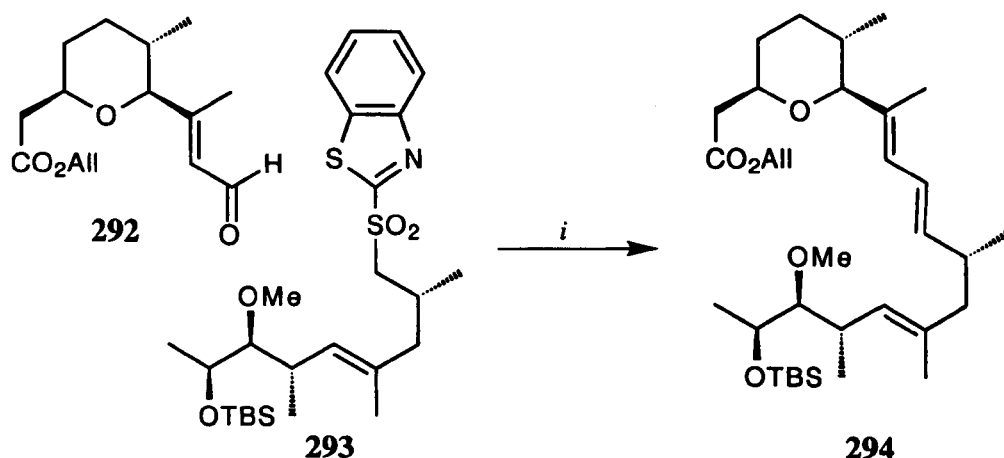
Due to the difficulties experienced with installing the oxazole as a single unit *via* the dithiane lithiation approach, we decided to omit the oxazole at this stage and concentrate on elaborating the side chain (**40**) *via* the diene unit. We anticipated that we could make use of the highly versatile olefin fragment (**272**) that we had synthesised earlier. A few functional group manipulations would then allow us to investigate possible options for the two successive olefination reactions that we planned to use. We believed that the

trisubstituted olefin in **40** could be derived *via* a Wittig reaction with a stabilised ylid, resulting in high selectivity in favour of the desired *trans*-isomer. The Julia olefination seemed an attractive possibility for the construction of the second olefin unit giving rise to the diene (**40**). The classical Julia reaction developed by Marc Julia *et al*,¹²⁸ suffers from the need for three separate steps to facilitate olefin formation, including reductive removal of the arylsulfone moiety. Recently, Sylvestre Julia and co-workers reported a new one-pot modification of the Julia reaction by employing a benzothiazole sulfone moiety.¹²⁹ This variant had the great advantage that the intermediate hydroxy sulfones were, in most cases, unstable and underwent a series of transformations resulting in the expulsion of sulfur dioxide and the lithium derivative of 1,3-benzothiazol-2-one (**291**) with concomitant formation of the desired olefin product in one step (**Scheme 82**).



Scheme 82

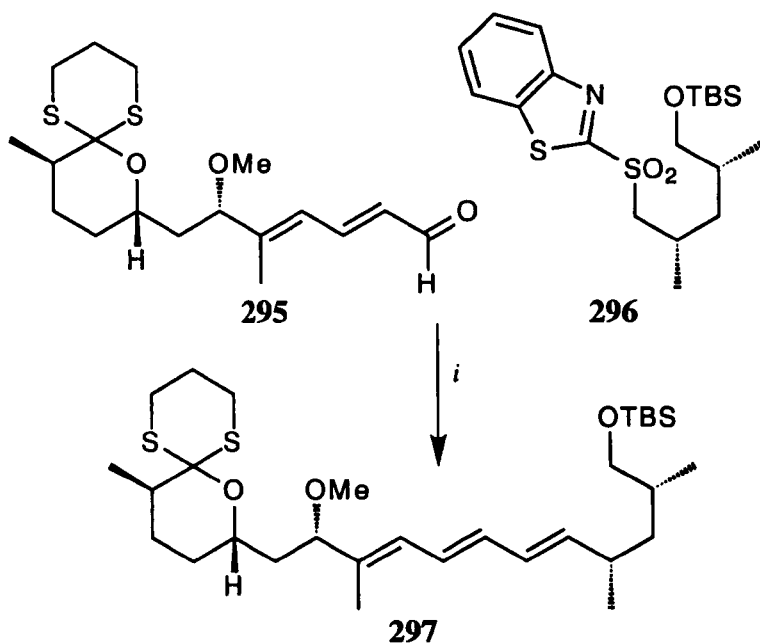
S. Julia *et al* studied this reaction in great detail with over 100 examples revealing some important limitations to this method.^{129b,c} They found that: 1) high stereoselectivities were only obtained in certain cases, *e.g.* the formation of conjugated dienes; and 2) some lithiated benzothiazolyl sulfones were unstable and underwent self condensation. On further investigation of this approach Kocienski *et al* used this method with success to form the (*E,E*)-diene unit in their studies towards the natural product herboxidiene¹³⁰ (Scheme 83) and also to form the triene unit in the immunosuppressant rapamycin¹³¹ (Scheme 84).



Reagents: *i*, LDA, THF, 65%.

Scheme 83

In both cases the union of the complex fragments proceeded excellently, to give the desired *trans*-geometry in good yield, with less than 5% of the undesired geometric isomer. Kocienski and co-workers also attempted the formation of the central triene olefin of rapamycin by this method,¹³¹ but found that the selectivity in this case was very poor, indicating that the nature of this reaction is both substrate and base dependant.



Reagents: *i*, LiHMDS, THF, 68%.

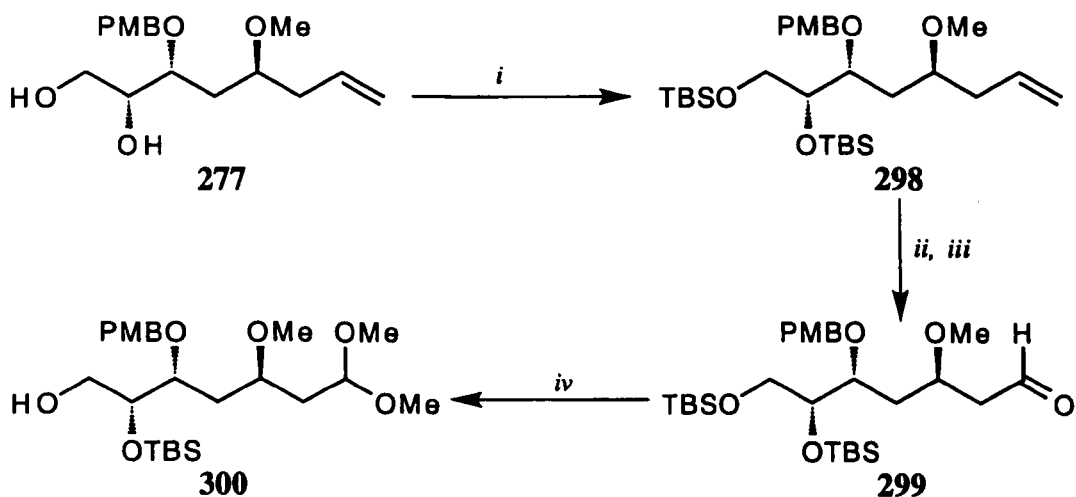
Scheme 84

Furthermore, Kocienski *et al* have extended this approach in the search for more general conditions applicable to isolated olefin formation with good selectivity.¹³² They have shown that phenyltetrazolyl sulfones participate in the reaction with aldehydes to give simple alkenes with good selectivity and high yield. Optimum conditions for this approach make use of the bases sodium or potassium hexamethyldisilazide in the more polar solvent dimethoxyethane. This work extends the scope of the Julia reaction and should be applicable to a wide variety of substrates as a useful alternative method for olefin construction.

Gratified by this successful literature precedent, we then embarked on our synthesis of the precursors for the coupling of **305** to **312**. We first had to address our protecting group strategy and differentiate between the primary and secondary alcohol groups in **277**. We also needed to transform the terminal olefin in **277** into a suitably protected unit, as we did not want to risk a selective olefin cleavage at a later stage. We anticipated that formation of a *bis*-silyl ether from the diol (**277**) would then allow for

selective cleavage of the primary silyl ether, thus differentiating between the two alcohols. For reasons of efficiency, we decided to cleave the olefin (**298**) to the aldehyde (**299**), which could be protected as a dimethyl acetal, so as to maintain this functionality at the aldehyde oxidation state.

Thus, protection of the diol (**277**) as the corresponding *bis-tert*-butyldimethyl silyl ether (**298**) followed by oxidative cleavage of the terminal double bond gave rise to the aldehyde (**299**). Treatment of the aldehyde (**299**) with camphorsulfonic acid in methanol resulted in acetal formation and to our delight simultaneous deprotection of the primary silyl ether leading to the alcohol (**300**) in a very appreciable 89% yield (Scheme 85).

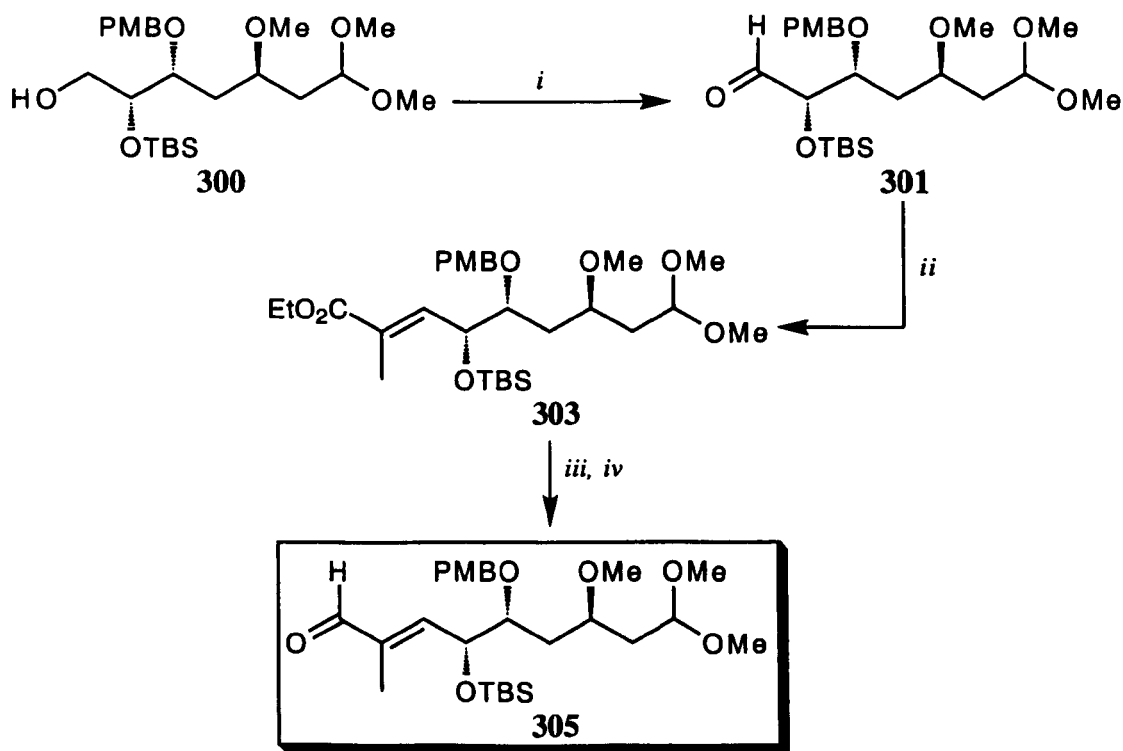


Reagents: *i*, TBS-OTf, Et₃N, CH₂Cl₂, 98%; *ii*, OsO₄, NMO, Acetone, H₂O; *iii*, NaIO₄, SiO₂, CH₂Cl₂, 94% (2 steps); *iv*, CSA, MeOH, 89%.

Scheme 85

Oxidation of the alcohol (**300**) with Dess-Martin periodinane,⁹⁰ buffered with 2,6-di-*tert*-butylpyridine gave the aldehyde (**301**), without any epimerisation of the α -chiral centre. When this oxidation was buffered with the less bulky base, 2,6-lutidine, we observed up to 10% of the epimerised aldehyde (**301**). Wittig reaction between the resulting aldehyde (**301**) and CH₃C(PPh₃)CO₂Et (**302**) then led exclusively to the (*E*)-

unsaturated ester (**303**) in a very pleasing 91% yield. Finally, the desired (*E*)- α,β -unsaturated aldehyde (**305**) was obtained by reduction of the ester (**303**) using DIBAL-H and oxidation of the product alcohol (**304**) with Dess-Martin periodinane⁹⁰ in excellent overall yield (**Scheme 86**).



Reagents: *i*, Dess-Martin periodinane, 2,6-di-*tert*-butylpyridine, CH₂Cl₂, 93%; *ii*, CH₃C(PPh₃)CO₂Et (**302**), C₆H₆, Δ , 91%; *iii*, DIBAL-H, CH₂Cl₂, 89%; *iv*, Dess-Martin periodinane, 2,6-lutidine, CH₂Cl₂, 94%.

Scheme 86

The stereochemical outcome of the Wittig reaction between the aldehyde (**301**) and the ylid (**302**) was determined as (*E*) by the observation of an NOE enhancement between the methylene protons and the olefinic proton, indicating that they are both on the same side and thus an (*E*) arrangement exists (**Figure 8**).

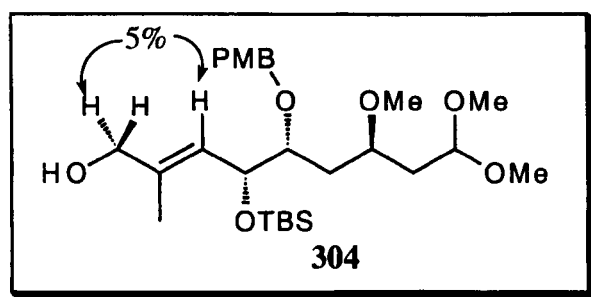
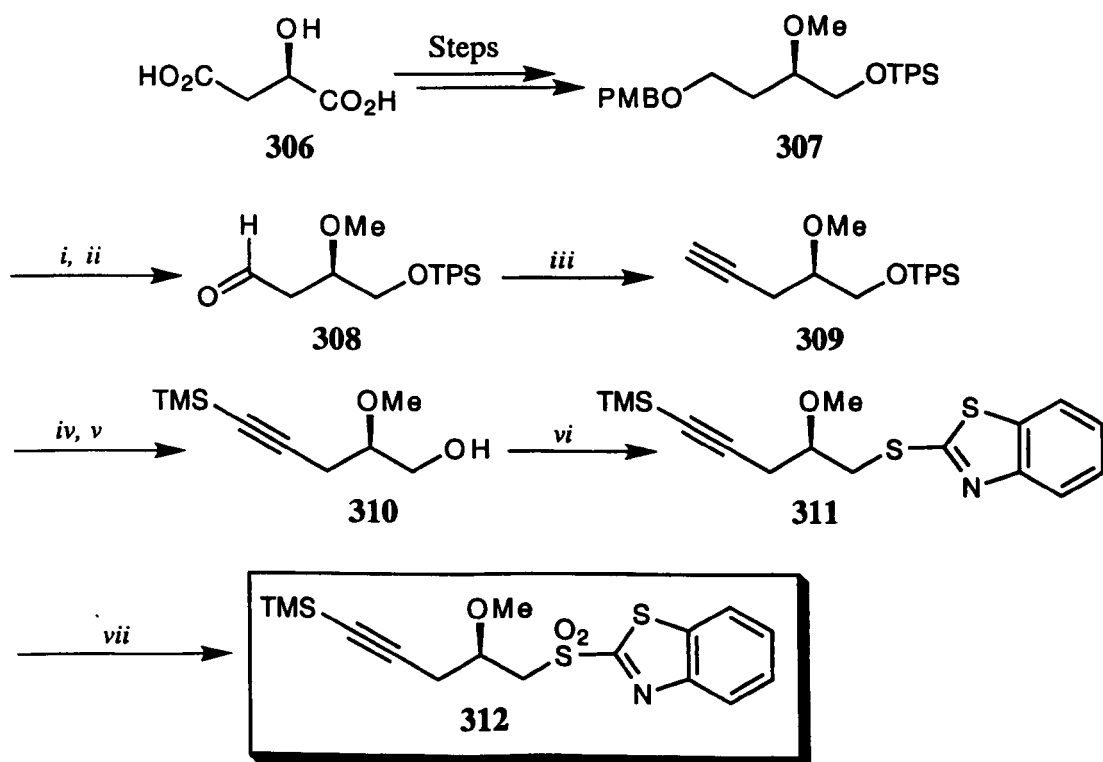


Figure 8: NOE analysis of the allylic alcohol (**304**).

The synthesis of the sulfone partner was exacted by my colleague Alleyn Plowright and again made use of chiral pool material as a source of the initial chirality. Thus, (*D*)-malic acid (**306**) was first converted into the differentially protected triol (**307**) using six straightforward steps in 43% overall yield. Deprotection of the PMB ether group in

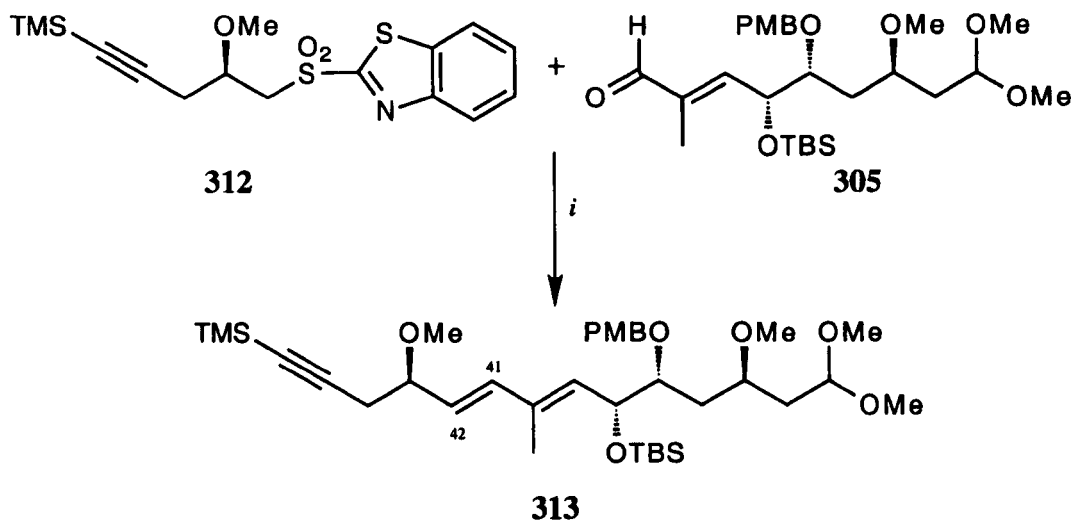


Reagents: *i*, DDQ, CH₂Cl₂, H₂O, 95%; *ii*, (COCl)₂, DMSO, Et₃N, CH₂Cl₂, 90%; *iii*, (MeO)₂PCHN₂, K^tBuO, THF, 75%; *iv*, TBAF, THF, 96%; *v*, TMS-Cl, *n*BuLi, THF, 70%; *vi*, 2-mercaptobenzothiazole, PPh₃, DEAD, CH₂Cl₂, 94%; *vii*, *m*-CPBA, NaHCO₃, THF, 85%.

Scheme 87

307 using DDQ,¹³³ followed by oxidation of the resulting primary alcohol under Swern conditions⁸⁸ next led to the aldehyde (**308**) which was then converted into the terminal acetylene (**309**) using Seyferth's reagent.¹³⁴ The primary alcohol function in **309** was unmasked and the terminal acetylene residue was then protected as the corresponding trimethylsilane derivative (**310**). Treatment of **310** with 2-mercaptobenzothiazole under Mitsunobu conditions next gave the sulfide (**311**), which on oxidation with *m*-CPBA finally gave the benzothiazole sulfone intermediate (**312**) as a stable crystalline solid (**Scheme 87**).

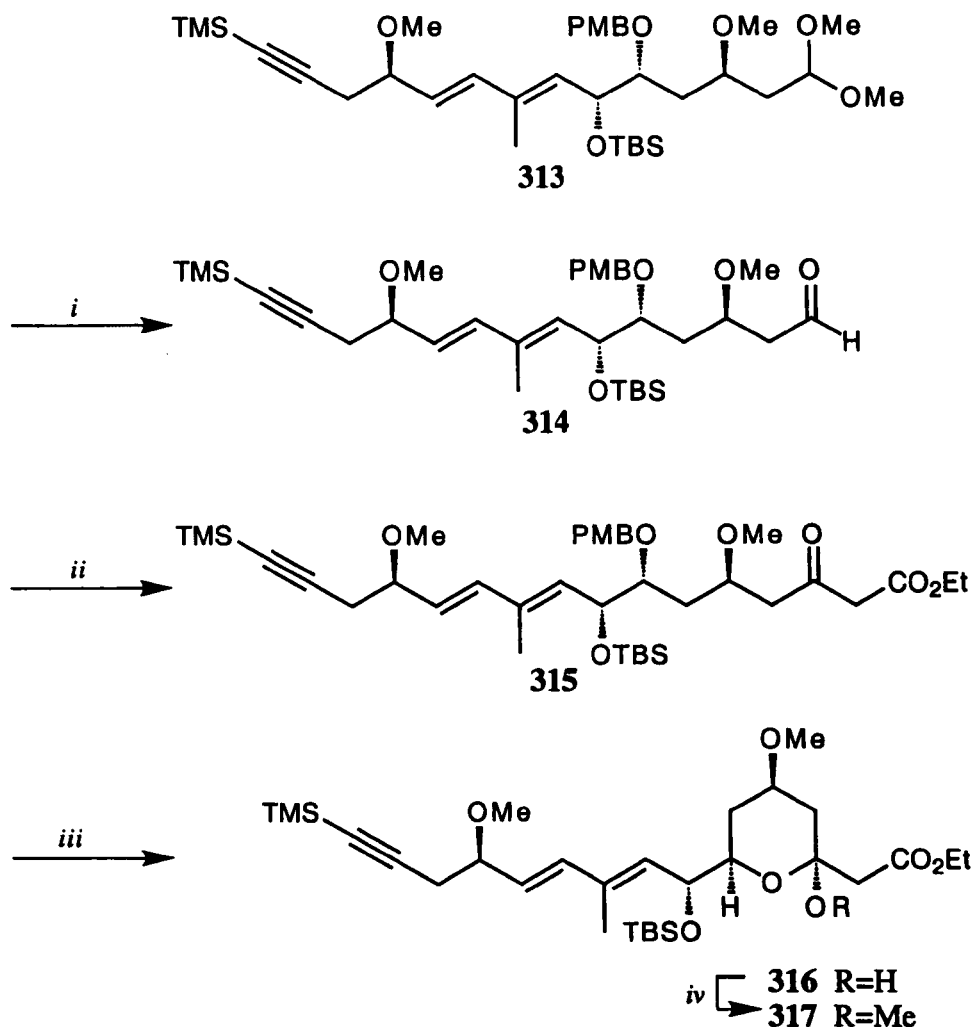
With the required fragments now available, we were ready to attempt the key one-pot Julia olefination step. Thus, deprotonation of the sulfone (**312**) using NaHMDS in THF at -78°C in the presence of the (*E*)-unsaturated aldehyde (**305**) resulted in stereoselective formation of the (*E,E*)-diene (**313**) in a satisfying 74% yield. The stereochemical outcome of the olefination was determined by examination of the olefinic coupling constants. We observed a coupling constant of 15.7Hz, across the newly formed C-41-C-42 olefin, indicating the desired (*E*)-geometry, which compared very favourably with phorboxazole A ($J_{\text{C-41-C-42}} = 15.7\text{Hz}$).^{10a} Approximately 5% of the undesired (*Z,E*)-isomer was also observed, but this could be readily removed by chromatography (**Scheme 88**).



Reagents: i, NaHMDS, THF, 74%.

Scheme 88

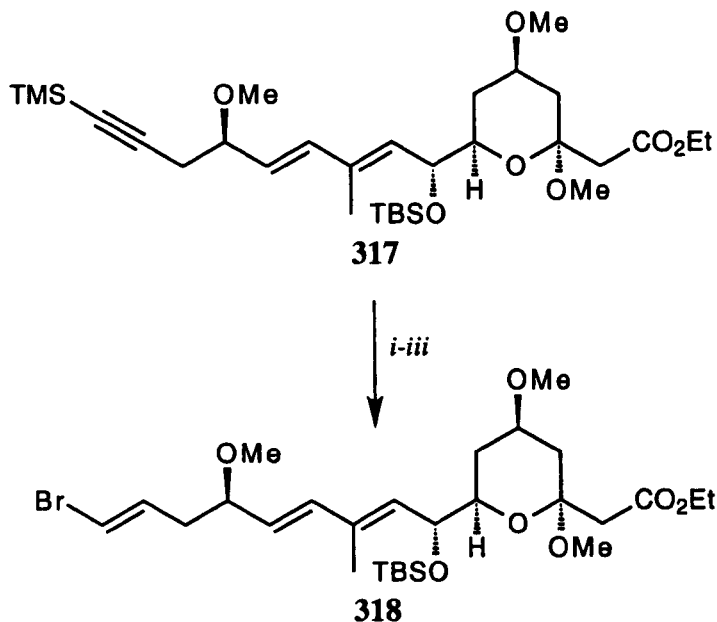
We were unable to deprotect the dimethyl acetal group in **313** under mild acidic conditions (PPTS, CSA or Amberlyst). However we were able to effect this transformation using the highly versatile reagent dimethylboron bromide,¹³⁵ to give the aldehyde (**314**) in an excellent 95% yield. Treatment of the aldehyde (**314**), under the conditions described by Roskamp *et al*,¹³⁶ with ethyl diazoacetate and catalytic tin(II) chloride next provided the β -keto ester (**315**). Removal of the PMB protecting group in **315** using DDQ in wet dichloromethane¹³³ resulted in spontaneous cyclisation of the intermediate δ -hydroxy ketone producing a single diastereomer of the cyclic *hemi*-acetal (**316**) in 90% yield (Scheme 89). Protection of the *hemi*-acetal (**316**) as the mixed methyl ketal (**317**) was achieved by exposure to a very mild acidic methanol solution. This compound (**317**) represented the complete carbon backbone of the side chain bearing an ester terminus, which is suitable for elaboration to the corresponding oxazole.



Reagents: *i*, Me_2BBr , Et_2O , 95%; *ii*, $\text{EtO}_2\text{CCHN}_2$, SnCl_2 , CH_2Cl_2 , 75%; *iii*, DDQ, CH_2Cl_2 , H_2O , 90%; *iv*, PPTS, MeOH , 60%.

Scheme 89

The synthesis of the vinyl bromide (**318**) was then completed by my colleague Alleyn Plowright, demonstrating the ability for vinyl bromide formation in the presence of a vast array of functionality. Deprotection of the terminal trimethylsilyl acetylene unit in **317**, followed by hydrostannylation and treatment of the intermediate vinylstannane with NBS in acetonitrile at 0°C gave the (*E*)-vinyl bromide (**318**), completing the C-31-C-46 side chain fragment of phorboxazole A (**4**) (Scheme 90).¹³⁷



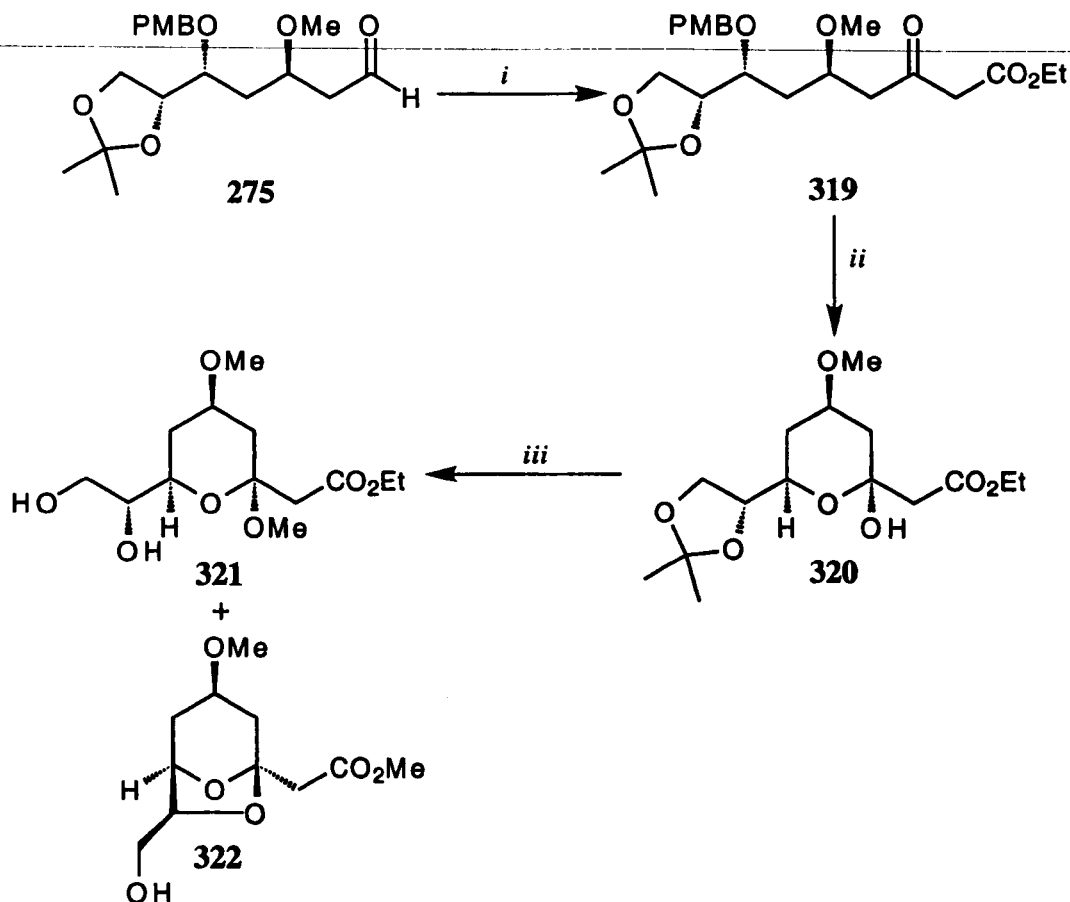
Reagents: i, AgNO₃, KCN, EtOH, 75%; ii, Bu₃SnH, AIBN, C₆H₆, Δ; iii, NBS, CH₃CN, 60% (2 steps).

Scheme 90

2.3.5 Oxazole Inclusion

Unfortunately due to shortage of material, we were unable to elaborate the ester in **317** to the oxazole unit. Instead we decided to modify our strategy slightly, so as to install the oxazole prior to the Wittig and Julia reactions. Throughout this approach we have made extensive use of the methods discussed previously for the assembly of the entire side-chain. Thus, from the aldehyde (**275**) we were able to elaborate the β-keto ester (**319**) in good yield using Roskamp's procedure.¹³⁶ Attempts to increase this yield by using Nomura's modification¹³⁸ using zirconium tetrachloride instead of tin(II) chloride, failed to improve the yield, resulting in decomposition of the aldehyde, possibly due to the necessity for a stoichiometric amount of Lewis acid. Treatment of **319** with DDQ then effected removal of the PMB group,¹³³ giving rise to the desired *hemi*-acetal (**320**) simultaneously as a single diastereomer. One pot deprotection of the acetonide and mixed methyl ketal formation was then achieved by exposure of the *hemi*-acetal (**320**) to a solution of PPTS in methanol. On a small scale this provided

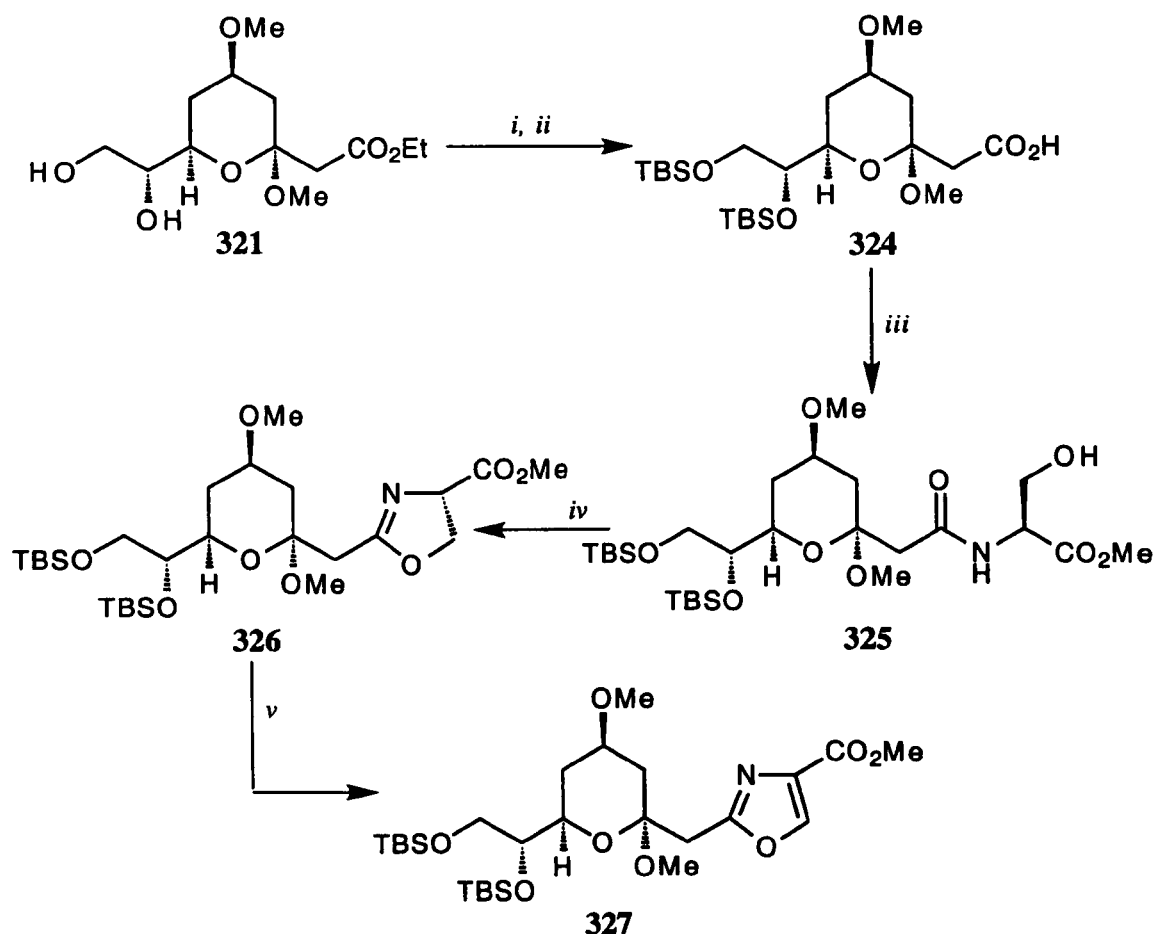
good yields of the desired diol (**321**), however on a larger scale, with prolonged exposure to acid, we observed up to 40% of a side-product which we have tentatively assigned as the [6,5]-bicycle (**322**), the result of an intramolecular ketalisation (Scheme 91).



Reagents: i, EtO₂CCHN₂, SnCl₂, CH₂Cl₂, 77%; ii, DDQ, CH₂Cl₂, H₂O, 80%; iii, PPTS, MeOH, 79%.

Scheme 91

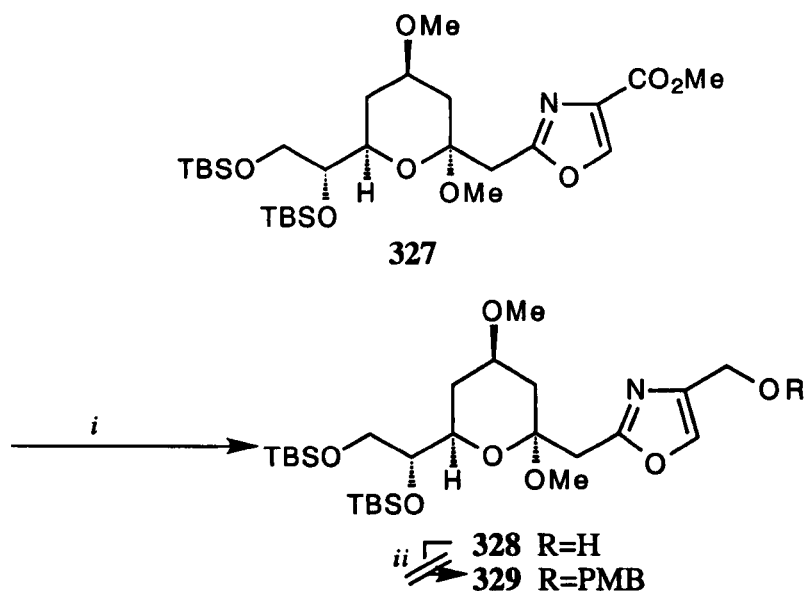
Protection of the diol (**321**) as the *bis*-silyl ether (**323**) and saponification of the ethyl ester with aqueous lithium hydroxide furnished the precursor (**324**) for oxazole formation. Amide formation was achieved in good yield, installing the hydroxy-amide (**325**), which was cyclised to the oxazoline (**326**) in 80% yield with DAST.⁸⁶ The oxazole (**327**) was finally obtained using the conditions of Williams *et al*,¹¹⁰ by treatment of the oxazoline (**326**) with bromotrichloromethane and DBU (Scheme 92).



Reagents: *i*, TBS-OTf, Et₃N, CH₂Cl₂, 82%; *ii*, LiOH, MeOH, H₂O; *iii*, L-serine-OMe.HCl, EDC, HOBT, Et₃N, THF, 73% (2 steps); *iv*, DAST, CH₂Cl₂, 80%; *v*, DBU, BrCCl₃, CH₂Cl₂, 82%.

Scheme 92

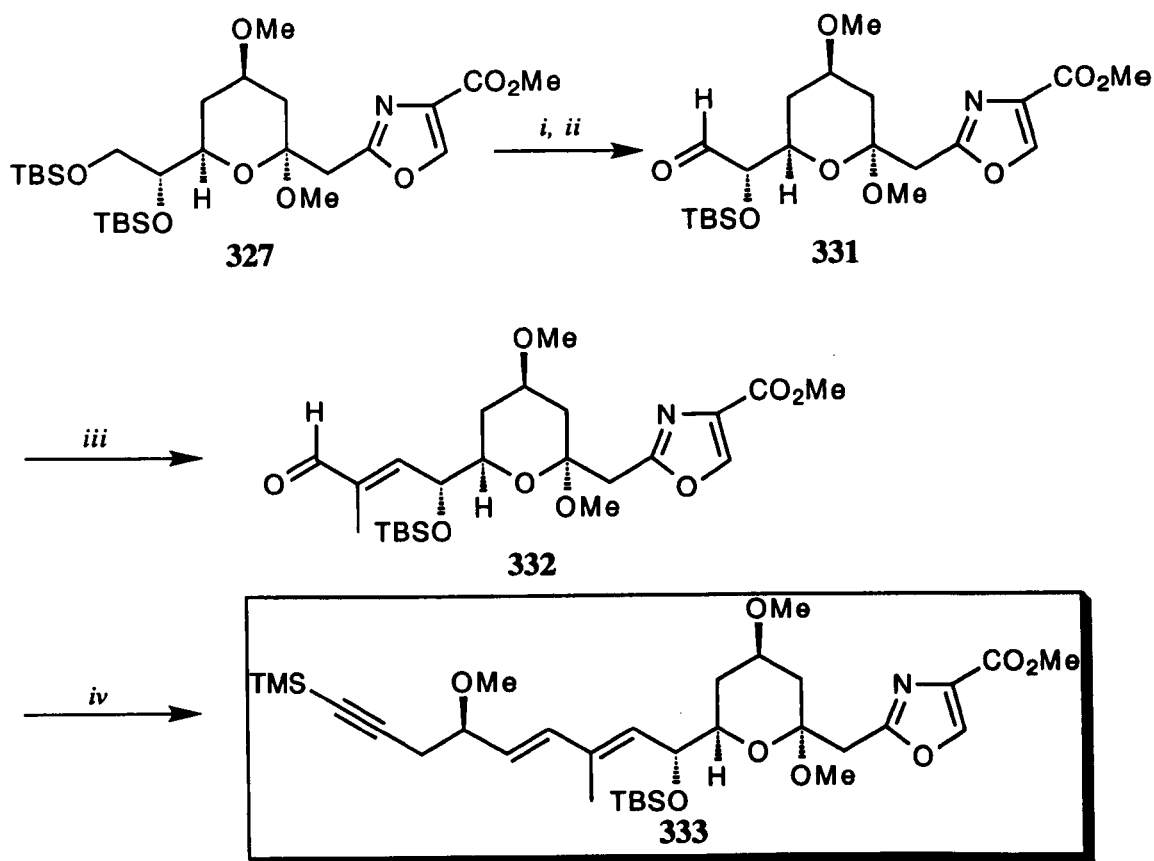
In order to follow our previous synthetic approach, we deemed it necessary to replace the ester moiety in **327** with a suitably protected alcohol. Given the functionality present in this fragment, and the reaction conditions that would have to be tolerated we gave careful consideration to our protecting group strategy. We had previously shown that a *p*-methoxybenzyl group would tolerate these reaction conditions, so we decided to reduce the ester (**327**) and protect it as the PMB ether (**329**). Reduction to the alcohol (**328**) was achieved in good yield. However we were unable to produce the desired PMB ether (**329**), and only decomposition of the alcohol was observed (Scheme 93).



Reagents: i, DIBAL-H, CH₂Cl₂, 87%; ii, K^tBuO, PMB-Cl, NBu₄I, THF.

Scheme 93

Rather than pursue this troublesome protection we decided to maintain the ester functionality and make use of the Wittig reagent CH₃C(PPh₃)CHO (**262**), so avoiding the subsequent reduction, oxidation steps to obtain the Julia precursor (**332**). Thus, once again the primary silyl ether was cleaved in acidic methanol, and the resulting alcohol (**330**) was oxidised with Dess-Martin periodinane⁹⁰ to give the aldehyde (**331**). We then attempted the Wittig reaction of the aldehyde (**331**) with the ylid (**262**). The reaction seemed to progress quite cleanly, but on workup we were dismayed to find that we had a very poor yield of the product (**332**), contaminated with some starting material, it also appeared that there was up to 10% epimerisation product. A difficult purification of this material gave an approximate yield of 25% of the unsaturated aldehyde (**332**), containing some contaminants. We then subjected this material to the Julia olefination conditions with the sulfone (**312**) and we were delighted to isolate a 6:1 ratio of isomers, which could be separated to give the desired (*E,E*)-1,3-diene (**333**) in 59% yield, displaying spectral characteristics very similar to that of phorboxazole A (**4**) (Scheme 94).



Reagents: *i*, CSA, MeOH, CH₂Cl₂, 59%; *ii*, Dess-Martin periodinane, 2,6-di-*tert*-butylpyridine, CH₂Cl₂, 90%; *iii*, CH₃C(PPh₃)CHO, C₆H₆, Δ, 25%; *iv*, NaHMDS, 312, THF, 59%.

Scheme 94

2.3.6 Conclusions

We have demonstrated the use of the recently developed one pot Julia olefination¹²⁹ as an extremely efficient method for the construction of highly oxygenated 1,3-dienes with good stereoselectivity and yield. Making use of chiral pool materials we were able to produce the desired Julia precursors in good overall yield. Furthermore, we have shown that an oxazole unit will survive the Julia olefination conditions, and this is a viable synthetic approach if the oxazole is to be included. Although a very poor yield in the penultimate Wittig step was observed, the approach did reduce the number of additional steps to (333) by four. We anticipate that both of these approaches to the

diene unit (40) will be important for final assembly of phorboxazole A from the three units (40), (41) and (42).

2.4 Research Summary

The main emphasis throughout this period of research has been towards the efficient construction of two subunits (40) and (42), resulting from the disconnection of phorboxazole A (Scheme 3). We initially sought to apply hetero Diels-Alder methodology to furnish the *cis*-tetrahydropyran present in the oxazole *bis*-pyran unit (42). We were encouraged by our early studies with simple oxazole aldehydes to give reasonable yields of oxazole *cis*-tetrahydropyrans and aimed to create a synthesis which would provide this fragment as a single enantiomer. This approach relied on a chiral oxazoline or oxazolidine aldehyde to provide the initial chirality, both ultimately derived from the amino acid serine. We were able to utilise Garner aldehyde (145) and obtain hetero Diels-Alder cycloadducts in modest yield which were readily scaled up. The initial cycloadduct was elaborated so that oxazole formation could be investigated. Under the recently described conditions of Wipf,⁵³ cyclodehydration of an intermediate amido-aldehyde led to the desired 2,4-disubstituted oxazole pyran in a reasonable yield. With this newly formed oxazole pyran we were able to demonstrate the synthetic utility of a Wadsworth-Emmons type coupling to form the C-19-C-20 *trans*-olefin of the macrolide in a very facile manner exhibiting high selectivity. We had been unable to prove the relative stereochemistry of the tetrahydropyran, formed by the hetero Diels-Alder reaction, until late in the synthetic sequence, and to our disappointment we determined it to have a *trans*- relative geometry. We believe that this is as a result of a large deviation in aldehyde substrate from our initial model studies. The use of the bulky Garner aldehyde prevents the diene approaching in an *endo* manner, as we postulated for the oxazole aldehyde, and thus the approach of the diene and the aldehyde is *exo*, resulting in the undesired *trans*-tetrahydropyran.

Studies were also undertaken to elaborate the *trans*-tetrahydropyran in **42**, by examining an intramolecular conjugate addition onto an unsaturated acrylate. Unfortunately we were unable to achieve *trans*:*cis* ratios which were sufficiently high enough to be synthetically useful, in most cases the more thermodynamically favoured *cis*-isomer prevailed. We were able to overcome this disappointing selectivity by utilising an alternative strategy. Using material that we had previously synthesised we were able to furnish a pyran oxonium ion precursor (**258**), treatment of **258** with Lewis acid and allyltrimethylsilane led to an excellent yield of a single diastereomer of a *trans*-tetrahydropyran. This approach can provide a very useful intermediate towards the synthesis of the *bis*-pyran unit (**42**) in reasonable quantities.

The C-27-C-46 side chain (**40**) provided yet another challenge *en route* to the vast structure of phorboxazole A. We were able to provide large quantities of a three chiral centred, pivotal intermediate (**272**), in a short sequence of steps from (*D*)-xylose. We initially examined the use of lithiated dithiane chemistry for installation of the oxazole unit, but found difficulties with this approach. We thus turned our attention to the formation of the C-39-C-42 diene unit prior to oxazole formation. Elaboration of **272** to an orthogonally protected aldehyde set the platform for the initial Wittig reaction, which provided a (*E*)-trisubstituted olefin in excellent yield and selectivity. This was then elaborated to an aldehyde for the key olefination reaction. We chose to make use of a modified Julia reaction for diene formation, and thus a benzothiazole sulphone was prepared from malic acid to incorporate the C-43 stereogenic centre. The Julia olefination between the aldehyde (**305**) and sulphone (**312**) gave the desired diene, once again with good yield and selectivity. In a short number of steps we were able to elaborate this through to the C-31-C-46 side chain unit, incorporating the vinyl bromide and hemi-acetal pyran moiety.

In an attempt to make this strategy more convergent we sought to install the oxazole unit prior to Julia olefination. We were able to take our pivotal intermediate (**272**) and

extend this to include the oxazole unit in a stepwise manner. Subsequent functional group manipulations were performed so that the olefination reactions could be attempted. Wittig reaction proceeded in low yield but remained unoptimised. This material was then subjected to the Julia olefination conditions and to our delight provided a good yield of the desired diene, representing the entire C-27-C-46 side chain unit. This work has demonstrated the scope of this Julia olefination reaction, and shown that it will tolerate much functionality and can be used as an important tool in the final assembly of the various subunits.

A concise synthesis of the side chain unit of phorboxazole A has been described. This and the previously published synthesis of the central pyran core⁶² gives two of the key fragments required for final assembly of phorboxazole A. Hopefully the research carried out towards the final subunit, the oxazole *bis*-pyran (**42**), described in this thesis will be valuable in future synthetic efforts towards this fragment, and allow for the rapid construction of **42**. Once all the various precursors are available it remains of my colleagues to draw on the wealth of literature available to devise a strategy for the successful coupling of these units and completion of a total synthesis of phorboxazole A.

3. EXPERIMENTAL

3.0 General Details

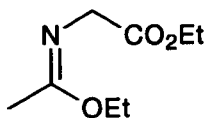
All melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were recorded in spectroscopic grade chloroform or dichloromethane on a Jasco DIP-370 polarimeter, $[\alpha]_D$ values are recorded in units of $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$. Ultraviolet spectra were recorded on a Philips PU 8700 spectrophotometer as solutions in spectroscopic grade ethanol, ϵ values are recorded in units of $\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$. Infrared spectra were obtained using a Perkin-Elmer 1600 series FT-IR instrument or a Nicolet Magna 550 instrument either as liquid films or as dilute solutions in spectroscopic grade chloroform. Proton nmr spectra were recorded on either a Bruker WM 250 (250MHz), a Bruker DPX 360 (360MHz), a Bruker AM 400 (400MHz), a Bruker DRX 500 (500MHz), a Varian Unity 300 (300MHz), a Varian Inova 400 (400MHz) or a Jeol EX 270 (270MHz) spectrometer as dilute solutions in deuteriochloroform, unless otherwise stated. The chemical shifts are quoted in parts per million (ppm) relative to residual chloroform as internal standard (δ 7.27) and the multiplicity of each signal is designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; quin., quintet; br, broad; m, multiplet; app., apparent; obs., obscured. All coupling constants are quoted in Hertz. Carbon-13 nmr spectra were recorded on either a Bruker DPX 360 (at 90.6MHz), a Bruker DRX 500 (at 125.8MHz), a Varian Unity 300 (at 75.5MHz) or a Jeol EX-270 (at 67.8MHz) instrument as dilute solutions in deuteriochloroform, unless otherwise stated. Chemical shifts are reported relative to internal chloroform standard (δ 77.0) on a broad band decoupled mode, and the multiplicities determined using a DEPT sequence. Where required, H-H COSY, H-C COSY, NOESY and NOE spectra were recorded on a Bruker DPX 360 (360MHz) or a Bruker DRX 500 (500MHz) instrument using standard Bruker software with no modifications. Mass spectra were recorded on a VG Autospec, a MM-701CF or a VG Micromass 7070E spectrometer using electron ionisation (EI) or fast atom bombardment (FAB) techniques. Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser.

Flash chromatography was performed on Merck silica gel 60 as the stationary phase and the solvents employed were either of analytical grade or were distilled before use. All reactions were monitored by tlc using Merck silica gel 60 F₂₅₄ precoated aluminium backed plates which were visualised with ultraviolet light and then with either acidic alcoholic vanillin solution, basic potassium permanganate solution, or acidic anisaldehyde solution.

Routinely, dry organic solvents were stored under nitrogen and/or over sodium wire. Other organic solvents were dried by distillation from the following: THF and benzene (potassium benzophenone ketyl), dichloromethane (calcium hydride) and methanol (magnesium methoxide). Other organic solvents and reagents were purified by the accepted literature procedures. Dess-Martin periodinane was prepared according to the modified procedure of Ireland and Liu.¹³⁹ All organic extracts were dried with magnesium sulfate unless otherwise stated. Solvent was removed on a Büchi rotary evaporator. Where necessary, reactions requiring anhydrous conditions were performed in a flame or oven dried apparatus under a nitrogen or argon atmosphere as stated.

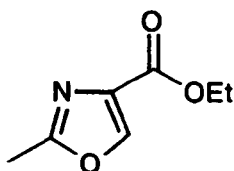
3.1 Hetero Diels-Alder Studies

Ethyl α -(ethoxyethylideneamino)acetate (109)⁷⁹



A cooled suspension (0°C) of ethylacetimidate hydrochloride (50g, 0.41mol) in diethyl ether (100ml) was shaken for 10min in a separating funnel with a cooled solution (0°C) of potassium carbonate (69.7g, 0.50mol) in water (75ml). The organic layer was separated and shaken with a cooled solution (0°C) of glycine ethyl ester hydrochloride (56.5g, 0.41mol) in water (75ml) for 10min. The organic layer was separated and washed with water (3 x 75ml) and brine (75ml), dried and concentrated *in vacuo* to give the imino ether (33.5g, 50%) as a colourless oil, which was used immediately without characterisation.

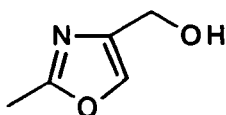
Ethyl 2-methyloxazole-4-carboxylate (111)⁷⁹



The imino ether (109) (57g, 0.33mol) was added dropwise over 20min to a stirred solution of potassium *tert* butoxide (40.4g, 0.36mol) in THF (250ml) at -20°C, under a nitrogen atmosphere. Ethyl formate (21g, 0.36mol) was added dropwise over 20min and the resulting mixture was stirred at -20°C for a further 1.5h. The solvent was removed *in vacuo* to leave the crude enolate salt as a yellow solid. Glacial acetic acid (100ml) was added to the enolate salt and the mixture was then heated under reflux for 30min, until all the solid had dissolved. After cooling to room temperature the resulting

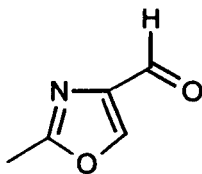
solution was diluted with water (100ml) and neutralised with solid sodium carbonate. The mixture was filtered and extracted with diethyl ether (3 x 250ml), the extracts were then dried and concentrated *in vacuo* to leave a brown oil. Distillation gave the oxazole as a pale yellow oil (28g, 55%); b.p. 118-120°C/13mmHg, which solidified on standing; m.p. 24-25°C; ν_{\max} (film) 3160, 2980, 1740, 1500 cm^{-1} ; δ_{H} (250MHz) 8.13 (s, 1H, Ox-H), 4.37 (q, J 7.1, 2H, CH_2CH_3), 2.51 (s, 3H, Ox- CH_3), 1.37 (t, J 7.1, 3H, CH_2CH_3); δ_{C} (67.8MHz) 162.2 (s), 161.1 (s), 143.6 (d), 133.3 (s), 61.0 (t), 14.1 (q), 13.7 (q).

(2-Methyl-oxazol-4-yl)-methanol (112)¹⁴⁰



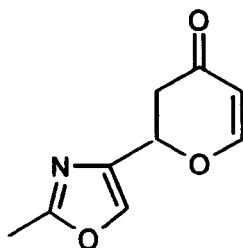
A solution of di-*isobutyl*aluminium hydride (107ml, 1.5M in toluene, 160mmol) was added dropwise over 1h to a solution of ethyl 2-methyloxazole-4-carboxylate (111) (10g, 64mmol) in dichloromethane (200ml) at -78°C, under a nitrogen atmosphere. Stirring was continued for 4h at -78°C and then the solution was allowed to warm to room temperature and stirred for a further 12h. The mixture was quenched with methanol and then stirred until the mixture solidified. Dichloromethane and magnesium sulfate were added, which resulted in the formation of a granular precipitate. The mixture was stirred for 1h, then filtered and the solid residue washed with dichloromethane (400ml). The filtrate was concentrated *in vacuo* to leave a yellow solid which was purified by chromatography on silica, eluting with ethyl acetate to give the alcohol (6.28g, 86%) which crystallised as a yellow solid; m.p. 49-50°C ($\text{Et}_2\text{O}/\text{Pet.}$), [Lit. m.p. 40-41°C]¹⁴⁰; ν_{\max} (soln., CHCl_3) 3400, 1710, 1583, 1102 cm^{-1} ; δ_{H} (250MHz) 7.49 (s, 1H, Ox-H), 4.55 (s, 2H, CH_2OH), 3.80 (br s, 1H, OH), 2.46 (s, 3H, Ox- CH_3); δ_{C} (67.8MHz) 162.7 (s), 140.6 (s), 135.3 (d), 56.4 (t), 14.2 (q).

2-Methyl-oxazole-4-carbaldehyde (113)¹⁴¹



Activated manganese dioxide (15.37g, 177mmol) was added in one portion to a solution of the oxazole alcohol (112) (2.0g, 17.7mmol) in dichloromethane (400ml). The solution was stirred at room temperature for 16h until all the starting material had been consumed. The mixture was then filtered through Celite and the filtrate was concentrated *in vacuo* to leave the aldehyde (1.67g, 85%) which crystallised as a white solid; m.p. 75-76°C (Et₂O/Hex.), [Lit. m.p. 71-73°C (Et₂O/Hex.)]¹⁴¹; ν_{max} (soln., CHCl₃) 2843, 1701, 1591, 1564cm⁻¹; δ_{H} (250MHz) 9.90 (s, 1H, CHO), 8.21 (s, 1H, Ox-H), 2.52 (s, 3H, Ox-CH₃); δ_{C} (67.8MHz) 183.6 (d), 162.9 (s), 144.7 (d), 140.8 (s), 13.7 (q).

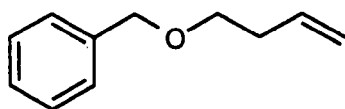
2-(2'-Methyl-oxazol-4'-yl)-2,3-dihydro-pyran-4-one (115)



2-Methyl-oxazole-4-carbaldehyde (113) (1.60g, 14.4mmol) followed by zinc chloride (1.96g, 14.4mmol) were added to a solution of *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (2.73g, 15.8mmol) in dry benzene (100ml), under a nitrogen atmosphere. The reaction was stirred at room temperature for 24h after which time a saturated solution of sodium bicarbonate (50ml) was added. The organic phase was separated and the aqueous layer was extracted with diethyl ether (4 x 75ml). The

combined extracts were dried and the solvent was removed *in vacuo* to leave a brown oil. Dichloromethane (40ml) and trifluoroacetic acid (3ml) were added to the crude product and the mixture stirred for 10min. A saturated solution of sodium bicarbonate (20ml) was then added and stirring continued for a further 10min. The organic layer was separated and the aqueous phase was extracted with dichloromethane (3 x 50ml), dried and concentrated *in vacuo* to leave a brown residue. The residue was purified by chromatography on silica, eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *dihydropyrone* (1.96g, 76%) which crystallised as a yellow solid; m.p. 87°C (EtOAc/Pet); ν_{\max} (soln., CHCl₃) 3683, 3619, 3028, 2976, 1674, 1594, 1522cm⁻¹; δ_{H} (250MHz) 7.57 (s, 1H, Ox-H), 7.38 (d, *J* 6.1, 1H, *H*-6), 5.49 (dd, *J* 6.1, 0.9, 1H, *H*-5), 5.42 (dd, *J* 13.1, 3.9, 1H, *H*-2), 3.03 (dd, *J* 16.9, 13.1, 1H, *H*-3), 2.70 (ddd, *J* 16.9, 3.9, 1.1, 1H, *H*-3), 2.48 (s, 3H, Ox-CH₃); δ_{C} (67.8MHz) 192.0 (s), 162.5 (d), 137.0 (s), 135.9 (d), 135.9 (s), 107.5 (d), 73.6 (d), 40.3 (t), 13.9 (q); *m/z* (EI) Found: 179.0592 (M⁺ C₉H₉NO₃ requires 179.0582); Found: C, 60.0; H, 4.9; N, 7.3%, C₉H₉NO₃ requires C, 60.4; H, 5.1; N, 7.8%.

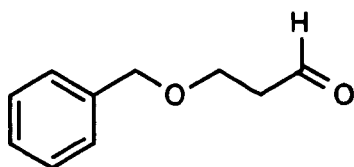
3-Benzyloxy-but-1-ene (121)¹⁴²



3-Buten-1-ol (10.0g, 139mmol) was added dropwise over 15min to a stirred suspension of sodium hydride (6.1g, 60wt% in oil, 153mmol) (washed previously with pentane) and tetrabutylammonium iodide (2.5g, 6.9mmol) in THF (500ml) at 0°C, under a nitrogen atmosphere. The suspension was stirred at 0°C for 30min and then benzyl bromide (16.5ml, 139mmol) was added dropwise over 15min. The suspension was allowed to warm to room temperature and stirred for 24h. The reaction was quenched with water (30ml) and the solvent removed *in vacuo*. An aqueous solution of brine (300ml, 50%) was added to the residue which was then extracted with ethyl

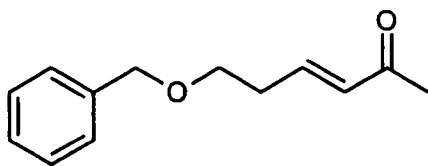
acetate (3 x 250ml), the combined extracts were then dried and concentrated *in vacuo* to give the benzyl ether as a yellow oil (22.0g, 98%), which was used without further purification; ν_{\max} (film) 3065, 2926, 2855, 1641, 1454, 1361, 1101 cm^{-1} ; δ_{H} (360MHz) 7.37-7.27 (m, 5H, Ar), 5.92-5.81 (m, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$), 5.15-5.04 (m, 2H, $\text{CH}=\text{CH}_2$), 4.54 (s, 2H, OCH_2Ar), 3.54 (t, J 6.8, 2H, CH_2OBn), 2.43 (td, J 6.8, 6.8, 1.4, 1.4, 2H, $\text{CH}_2\text{CH}=\text{CH}_2$); δ_{C} (90MHz) 138.4 (s), 135.2 (s), 128.3 (d), 127.6 (d), 127.5 (d), 116.3 (t), 72.8 (t), 69.5 (t), 34.2 (t); m/z (EI) Found: 162.1040 (M^+ $\text{C}_{11}\text{H}_{14}\text{O}$ requires 162.1045).

3-Benzyloxy-propionaldehyde (122)¹⁴³



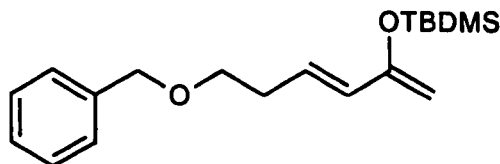
A stirred solution of 3-benzyloxy-but-1-ene (121) (21.0g, 130mmol) in dichloromethane (400ml) at -78°C was treated with a flux of ozone until the solution went pale blue (approximately 5h). Oxygen was bubbled through the solution for 10min until the solution decolourised and triphenylphosphine (34.0g, 130mmol) was then added in one portion. The solution was allowed to warm up to room temperature over 1h and then stirred for 12h. The solution was then concentrated *in vacuo* to leave a solid residue which was filtered through a short pad of silica, eluting with 20% ethyl acetate in petroleum ether (b.p. $40\text{--}60^\circ\text{C}$). The residue was then distilled under reduced pressure to give the aldehyde (15.6g, 74%) as a pale yellow oil, b.p. $94\text{--}96^\circ\text{C}/1\text{mmHg}$; ν_{\max} (film) 2862, 2731, 1724, 1096 cm^{-1} ; δ_{H} (360MHz) 9.78 (t, J 1.8, 1H, CH_2CHO), 7.37-7.33 (m, 5H, Ar), 4.54 (s, 2H, OCH_2Ar), 3.81 (t, J 6.1, 2H, CH_2OBn), 2.68 (td, J 6.1, 1.8, 2H, CH_2CHO); δ_{C} (90MHz) 200.9 (s), 137.7 (s), 128.2 (d), 127.5 (2x d), 73.0 (t), 63.6 (t), 43.6 (t); m/z (EI) Found: 164.0834 (M^+ $\text{C}_{10}\text{H}_{12}\text{O}_2$ requires 164.0837).

(E)-6-Benzyloxy-hex-3-en-2-one (123)¹⁴⁴



1-Triphenylphosphoranylidene-2-propanone (0.87g, 2.74mmol) was added in one portion to a stirred solution of 3-benzyloxy-propionaldehyde (122) (0.45g, 2.74mmol) in dichloromethane (10ml) under a nitrogen atmosphere. The solution was stirred at room temperature for 22h and then concentrated *in vacuo* to leave a yellow residue. The residue was purified by chromatography on silica, eluting with 10% ethyl acetate in petroleum ether (b.p. 40-60°C) to give the ketone (0.53g, 95%) as a colourless oil; ν_{\max} (film) 3030, 2859, 1695, 1674, 1099 cm^{-1} ; δ_{H} (400MHz) 7.35-7.23 (m, 5H, Ar), 6.80 (dt, J 16.0, 6.8, 1H, $\text{HC}=\text{CHCH}_2$), 6.11 (dt, J 16.0, 1.0, 1H, $\text{OCC}=\text{CH}$), 4.51 (s, 2H, OCH_2Ar), 3.58 (t, J 6.3, 2H, CH_2OBn), 2.51 (tdd, J 6.4, 6.4, 1.0, 2H, $\text{CH}=\text{CHCH}_2$), 2.22 (s, 3H, CH_3CO); δ_{C} (67.8MHz) 198.4 (s), 144.8 (d), 137.9 (s), 132.5 (d), 128.3 (d), 127.6 (2x d), 72.9 (t), 68.1 (t), 32.7 (t), 26.7 (q); m/z (EI) Found: 204.1160 (M^+ $\text{C}_{13}\text{H}_{16}\text{O}_2$ requires 204.1150); Found: C, 75.8; H, 7.9%, $\text{C}_{13}\text{H}_{16}\text{O}_2$ requires C, 76.4; H, 7.9%.

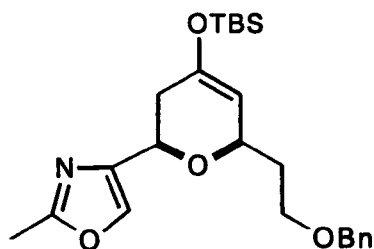
(E)-6-(Benzyloxy)-2-(tert-butyldimethyl-silanyloxy)hexa-1,3-diene (118)⁸³



Triethylamine (0.27ml, 1.91mmol) was added to a solution of (E)-6-benzyloxy-hex-3-en-2-one (123) (0.30g, 1.47mmol) in dichloromethane (10ml) at 0°C, under a nitrogen atmosphere. The solution was stirred for 10min and then *tert*-butyldimethylsilyl triflate

(0.50ml, 2.2mmol) was added dropwise over 1min. The solution was allowed to warm to room temperature and stirred for 2h. Water (20ml) was added and the biphasic mixture was extracted with dichloromethane (3 x 20ml), the combined extracts were then dried (Na_2SO_4) and concentrated *in vacuo*. The resulting oil was purified by filtration through a short plug of silica, eluting with petroleum ether (b.p. 40-60°C) to give the diene (0.47g, 100%) as a yellow oil; ν_{max} (film) 2955, 2856, 1593, 1319, 1254, 1027 cm^{-1} ; δ_{H} (400MHz) 7.36 (m, 5H, Ar), 6.04 (m, 1H, $\text{HC}=\text{CHCH}_2$), 5.97 (d, J 15.3, 1H, $\text{HC}=\text{CHCH}_2$), 4.54 (s, 2H, OCH_2Ar), 4.25 (d, J 5.9, 2H, $\text{CH}_2\text{COTBSCH}$), 3.56 (t, J 6.8, 2H, CH_2OBn), 2.45 (td, J 6.8, 6.7, 2H, $\text{CH}=\text{CHCH}_2$), 1.00 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 0.20 (s, 6H, $\text{Si}(\text{CH}_3)_2$); δ_{C} (67.8MHz) 154.9 (s), 138.0 (s), 129.6 (d), 128.3 (d), 128.2 (d), 127.7 (d), 127.6 (d), 94.4 (t), 72.9 (t), 69.7 (t), 32.6 (t), 25.8 (q), 18.3 (s), -4.7 (q); m/z (FAB) Found: 317.1948 ($[\text{M}-\text{H}]^+$ $\text{C}_{19}\text{H}_{29}\text{O}_2\text{Si}$ requires 317.1937).

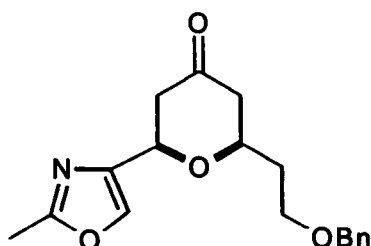
(2*R, 6*R**)-4'-[6-(2''-Benzyloxy-ethyl)-4-(*tert*-butyl-dimethyl-silanyloxy)-3,6-dihydro-2*H*-pyran-2-yl]-2'-methyl-oxazole (124)**



Boron trifluoride diethyl etherate (44 μ l, 0.36mmol) was added dropwise to a solution of the diene (118) (105mg, 0.33mmol) and the aldehyde (113) (40mg, 0.36mmol) in diethyl ether (5ml) at -78°C, under an argon atmosphere. The solution was stirred at -78°C for 1h and then allowed to warm to room temperature over a further 1h. Triethylamine (2 drops) and water (10ml) were then added and the biphasic mixture was extracted with ethyl acetate (3 x 15ml), the combined extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to leave a yellow oil. The oil was purified by

chromatography on silica, eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *dihydropyran* (85mg, 60%) as a colourless oil; ν_{\max} (soln., CHCl_3) 2930, 2856, 1670, 1579, 1362, 1096, 893 cm^{-1} ; δ_{H} (360MHz) 7.46 (d, J 1.0, 1H, Ox- H), 7.33-7.28 (m, 5H, Ar), 4.86 (t, J 1.6, 1H, H -5), 4.60 (ddd, J 11.0, 3.5, 1.0, 1H, H -2), 4.51 (s, 2H, OCH_2Ar), 4.50-4.47 (m, 1H, H -6), 3.70-3.58 (m, 2H, CH_2OBn), 2.49-2.43 (m, 1H, H -3), 2.45 (s, 3H, Ox- CH_3), 2.22 (dt, J 16.4, 2.9, 1H, H -3), 1.90 (dd, J 6.7, 6.4, 2H, $\text{CH}_2\text{CH}_2\text{OBn}$), 0.92 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 0.15 (s, 3H, SiCH_3), 0.14 (s, 3H, SiCH_3); δ_{C} (90MHz) 161.6 (s), 148.3 (s), 141.2 (s), 138.5 (s), 134.6 (d), 128.3 (d), 127.6 (d), 127.4 (d), 106.1 (d), 72.9 (t), 72.1 (d), 69.7 (d), 66.8 (t), 36.4 (t), 34.8 (t), 25.6 (q), 17.9 (s), 13.9 (q), -4.3 (q), -4.7 (q); m/z (EI) Found: 430.2408 ($[\text{MH}]^+$ $\text{C}_{24}\text{H}_{36}\text{NO}_4\text{Si}$ requires 430.2414).

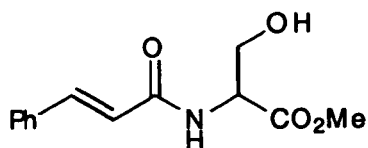
(2*R, 6*R**)-6-(2''-Benzyloxy-ethyl)-2-(2'-methyl-oxazol-4'-yl)-tetrahydro-pyran-4-one (125)**



Tetrabutylammonium fluoride hydrate (84mg, 0.27mmol) was added in one portion to a solution of the dihydropyran (124) (76mg, 0.18mmol) in THF (5ml) at room temperature. The solution was stirred for 5min and then a saturated solution of ammonium chloride (10ml) was added and the solvent was removed *in vacuo*. The residue was extracted with ethyl acetate (3 x 15ml), the combined extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to leave a yellow oil. The oil was purified by chromatography on silica, eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *ketone* (39mg, 70%) as a colourless oil; ν_{\max} (soln., CHCl_3) 2926, 2864, 1715, 1584, 1355, 1099 cm^{-1} ; δ_{H} (360MHz) 7.48 (s, 1H, Ox- H), 7.36-7.26 (m,

5H, Ar), 4.62 (dd, J 11.8, 2.8, 1H, H -2), 4.50 (app. q, J 12.0, 2H, OCH_2Ar), 4.00-3.93 (m, 1H, H -6), 3.68-3.55 (m, 2H, CH_2OBn), 2.81 (dd, J 14.7, 11.8, 1H, H -3 $_{ax}$), 2.59 (d app. t, J 14.7, 2.4, 1H, H -3 $_{eq}$), 2.51-2.36 (obs. m, 5H, H -5, Ox-CH_3), 2.09-2.00 (m, 1H, CHHCH_2OBn), 1.92-1.83 (m, 1H, CHHCH_2OBn); δ_{C} (90MHz) 206.1 (s), 162.1 (s), 139.8 (s), 138.2 (s), 135.0 (s), 128.4 (d), 127.6 (2x d), 74.5 (d), 73.0 (t), 71.6 (d), 66.0 (t), 47.6 (d), 46.2 (t), 36.3 (t), 14.0 (q); m/z (EI) Found: 315.1477 (M^+ $\text{C}_{18}\text{H}_{21}\text{NO}_4$ requires 315.1471).

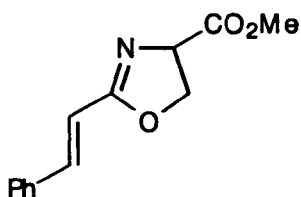
(*E*)-3-Hydroxy-2-(3'-phenyl-acryloylamino)-propionic acid methyl ester (131)¹⁴⁵



Triethylamine (12.8ml, 92.1mmol) was added to a suspension of *dl*-serine methyl ester hydrochloride (4.80g, 30.7mmol) in THF (200ml) at 0°C, under a nitrogen atmosphere. The suspension was stirred for 15min and then cinnamic acid (4.09g, 27.6mmol) was added in one portion. After a further 5min, 1-hydroxybenzotriazole (5.20g, 38.4mmol) was added, followed by 1,3-dicyclohexylcarbodiimide (8.90g, 43.0mmol) and the resulting suspension was stirred for 15h while warming to room temperature. The suspension was filtered, and the filtrate was concentrated *in vacuo*. The residue was taken up in ethyl acetate (100ml) and washed with a saturated solution of sodium bicarbonate (3 x 50ml). The organic phase was dried and concentrated *in vacuo* to leave a brown residue. The residue was purified by chromatography on silica, eluting with 40% ethyl acetate in petroleum ether (b.p. 40-60°C), increasing to 100% ethyl acetate, to give the hydroxy-amide (5.35g, 78%) as a waxy solid; m.p. 96-97°C (Tol./DCM), [Lit. m.p. 94-95°C (EtOAc)]¹⁴²; ν_{max} (soln., CHCl_3) 3421, 2956, 1741, 1668, 1629, 1503, 1356 cm^{-1} ; δ_{H} (400MHz) 7.62 (d, J 15.7, 1H, PhCH=CH), 7.46-7.43 (m, 2H, Ar), 7.34-7.29 (m, 3H, Ar), 7.09 (d, J 8.6, 1H, NH), 6.53 (d, J 15.7,

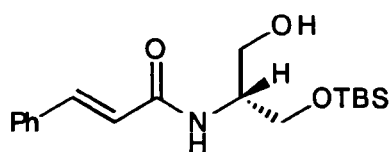
1H, PhCH=CH), 4.83-4.79 (m, 1H, CHCO₂CH₃), 4.05 (dd, *J* 11.3, 3.8, 1H, CHHOH), 3.97 (dd, *J* 11.3, 3.3, 1H, CHHOH), 3.75 (s, 3H, CO₂CH₃); δ_C (67.8MHz) 171.2 (s), 166.7 (s), 141.9 (d), 134.4 (s), 129.8 (d), 128.7 (d), 127.9 (d), 119.9 (d), 62.7 (t), 55.0 (d), 52.6 (q); *m/z* (EI) Found: 249.1013 (M⁺ C₁₃H₁₅NO₄ requires 249.1001); Found: C, 62.8; H, 6.1; N, 5.7%, Calc. for C₁₃H₁₅NO₄: C, 62.6; H, 6.1; N, 5.6%.

(*E*)-2-Styryl-4,5-dihydro-oxazole-4-carboxylic acid methyl ester (132)



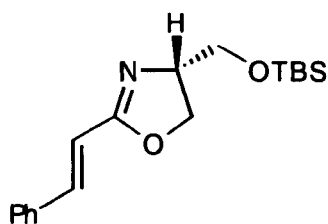
Diethylaminosulfur trifluoride (0.35ml, 2.65mmol) was added dropwise to a solution of the hydroxy amide (131) (600mg, 2.41mmol) in dichloromethane (10ml) at -78°C, under a nitrogen atmosphere. The solution was stirred at -78°C for 2h and then an aqueous solution of ammonium hydroxide (10ml, 4M) and ice (10g) were added. The biphasic mixture was allowed to warm to room temperature and then extracted with dichloromethane (3 x 30ml), the combined extracts were then dried (Na₂SO₄) and concentrated *in vacuo* to leave a brown oil. The oil was purified by chromatography on silica, eluting with 40% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *oxazoline* (480mg, 86%) as a colourless oil; ν_{\max} (soln., CHCl₃) 2955, 2910, 1731, 1650, 1632, 1608, 1366, 1071, 992, 973cm⁻¹; δ_H (360MHz) 7.48-7.45 (m, 2H, Ar), 7.41 (d, *J* 16.3, 1H, PhCH=CH), 7.39-7.33 (m, 3H, Ar), 6.65 (d, *J* 16.3, 1H, PhCH=CH), 4.88 (dd, *J* 10.5, 7.9, 1H, CHCO₂CH₃), 4.60 (dd, *J* 8.7, 7.9, 1H, CHHO), 4.50 (dd, *J* 10.5, 8.7, 1H, CHHO), 3.80 (s, 3H, CO₂CH₃); δ_C (67.8 MHz) 171.4 (s), 165.9 (s), 141.3 (d), 134.7 (s), 129.7 (d), 128.7 (d), 127.5 (d), 114.1 (d), 69.0 (t), 68.2 (d), 52.6 (q); *m/z*: (EI) Found: 231.0895 (M⁺ C₁₃H₁₃NO₃ requires 231.0895).

(1*R*, E)-N-[2-(*tert*-Butyl-dimethyl-silanyloxy)-1-hydroxy methyl-ethyl-3'-phenyl-acrylamide (138)



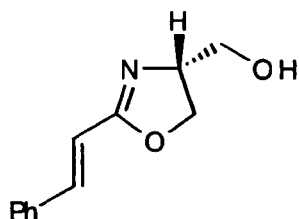
4-Methylmorpholine (21.2ml, 193mmol) was added to a solution of the amine (137)⁸⁷ (11.4g, 55.5mmol) in THF (300ml) at 0°C, under a nitrogen atmosphere. The solution was stirred for 15min and then cinnamic acid (9.50g, 64.3mmol) was added in one portion. After a further 5min, 1-hydroxybenzotriazole (10.9g, 80.4mmol) was added, followed by 1,3-dicyclohexylcarbodiimide (18.6g, 90.0mmol) and the resultant suspension was stirred for 18h while warming to room temperature. The suspension was filtered, and the filtrate was concentrated *in vacuo*, the residue was taken up in ethyl acetate (250ml). The organic phase was washed with a saturated solution of sodium bicarbonate (2 x 250ml), citric acid (2 x 200ml) and brine (2 x 200ml). The organic phase was dried and concentrated *in vacuo* to leave a solid residue. The residue was purified by chromatography on silica, eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), increasing gradually to 100% ethyl acetate, to give the *hydroxy-amide* (14.0g, 75%) as a yellow oil; $[\alpha]_D = -25.6$ ($c = 1.6$, CHCl_3); ν_{max} (soln., CHCl_3) 3626, 3430, 2930, 2858, 1666, 1626, 1074 cm^{-1} ; δ_{H} (360MHz) 7.64 (d, J 15.7, 1H, $\text{PhCH}=\text{CH}$), 7.52-7.49 (m, 2H, Ar), 7.38-7.34 (m, 3H, Ar), 6.44 (d, J 15.7, 1H, $\text{PhCH}=\text{CH}$), 6.40 (br d, J 7.7, 1H, NH), 4.14-4.10 (m, 1H, NHCH), 3.94 (dd, J 11.2, 4.2, 1H, CHHOTBS), 3.91-3.83 (m, 2H, CH_2OH), 3.74 (dd, J 11.2, 4.5, 1H, CHHOTBS), 0.92 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 0.10 (s, 3H, SiCH_3), 0.09 (s, 3H, SiCH_3); δ_{C} (90MHz) 166.2 (s), 141.5 (d), 134.7 (s), 129.7 (d), 128.8 (d), 127.8 (d), 120.3 (d), 63.9 (t), 63.8 (t), 52.0 (d), 25.8 (q), 18.2 (s), -5.5 (q), -5.6 (q); m/z (EI) Found: 260.1108 ($[\text{M}-t\text{Bu}-\text{H}_2\text{O}]^+$ $\text{C}_{14}\text{H}_{18}\text{NO}_2\text{Si}$ requires 260.1107).

(4*R*, *E*)-4-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-styryl-4,5-dihydro-oxazole (139)



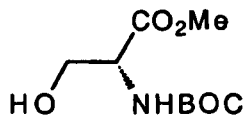
Diethylaminosulfur trifluoride (3.0ml, 22.5mmol) was added dropwise over 20min to a solution of the hydroxy-amide (138) (5.8g, 17.3mmol) in dichloromethane (100ml) at -78°C , under a nitrogen atmosphere. The solution was stirred at -78°C for 2h and then an aqueous solution of ammonium hydroxide (10ml, 4M) and ice (20g) were added. The biphasic mixture was allowed to warm to room temperature and then extracted with dichloromethane (3 x 70ml), the combined extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to leave a brown oil. The oil was purified by chromatography on silica, eluting with 40% ethyl acetate in petroleum ether (b.p. $40\text{--}60^{\circ}\text{C}$), to give the oxazoline (4.2g, 77%) as a yellow oil; $[\alpha]_{\text{D}} = +56.9$ ($c = 2.2$, CHCl_3); ν_{max} (soln., CHCl_3) 2930, 2858, 1653, 1608, 1352, 1099, 987, 973cm^{-1} ; δ_{H} (360MHz) 7.49-7.46 (m, 2H, Ar), 7.38-7.32 (m, 4H, Ar, $\text{PhCH}=\text{CH}$), 6.62 (d, J 16.3, 1H, $\text{PhCH}=\text{CH}$), 4.36-4.28 (m, 3H, CH_2OTBS , $H-4$), 3.87-3.83 (m, 1H, $H-5$), 3.63-3.59 (m, 1H, $H-5$), 0.88 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 0.07 (s, 3H, SiCH_3), 0.06 (s, 3H, SiCH_3); δ_{C} (90MHz) 164.4 (s), 139.9 (d), 135.2 (s), 129.3 (d), 128.7 (d), 127.4 (d), 115.5 (d), 69.9 (t), 68.0 (d), 64.9 (t), 25.7 (q), 18.1 (s), -5.4 (2x q); m/z (EI) Found: 317.1812 (M^+ $\text{C}_{18}\text{H}_{27}\text{NO}_2\text{Si}$ requires 317.1811); Found: C, 68.1; H, 8.7; N, 4.3%, $\text{C}_{18}\text{H}_{27}\text{NO}_2\text{Si}$ requires C, 68.1; H, 8.6; N, 4.4%.

(4*S*, *E*)-(2-Styryl-4,5-dihydro-oxazol-4-yl)-methanol (140)



Tetrabutylammonium fluoride hydrate (4.40g, 16.8mmol) was added in one portion to a solution of the oxazoline (**139**) (4.10g, 12.9mmol) in THF (100ml) at room temperature. The solution was stirred for 10min, then the solvent was removed *in vacuo* and the residue purified by chromatography on silica, eluting with ethyl acetate to give the *alcohol* (2.3g, 88%) which crystallised as a white solid; m.p. 88-90°C (Et₂O/Pet.); $[\alpha]_D = -42.5$ ($c = 2.3$, CHCl₃); ν_{\max} (soln., CHCl₃) 3592, 3207, 2906, 1658, 1608, 1365, 1103, 1070, 994, 973cm⁻¹; δ_H (360MHz) 7.33-7.29 (m, 5H, Ar), 7.21 (d, J 16.3, 1H, PhCH=CH), 6.52 (d, J 16.3, 1H, PhCH=CH), 4.42-4.31 (m, 3H, CH₂OH, *H*-4), 3.97 (dd, J 11.9, 2.5, 1H, *H*-5), 3.63 (dd, J 11.9, 3.2, 1H, *H*-5); δ_C (90MHz) 165.3 (s), 140.5 (d), 134.8 (s), 129.5 (d), 128.6 (d), 127.5 (d), 114.3 (d), 68.9 (t), 67.8 (d), 63.3 (t); m/z (EI) Found: 203.0957 (M^+ C₁₂H₁₃NO₂ requires 203.0946).

(2*R*)-2-*tert*-Butoxycarbonylamino-3-hydroxy-propionic acid methyl ester (143)¹⁴⁶

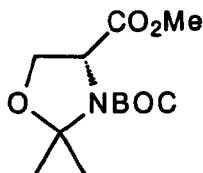


Acetyl chloride (100ml, 1.40mol) was added dropwise over 30min to methanol (400ml) at 0°C, under a nitrogen atmosphere. The solution was stirred for 10min before *D*-serine (50.0g, 0.47mol) was added in one portion and the solution was slowly heated to reflux. The mixture was heated under reflux for a further 2h, then cooled and

the solvent was removed *in vacuo* to give the crude ester hydrochloride (74.0g, 100%) as a white solid which was used without further purification.

Serine methyl ester hydrochloride (60.0g, 0.39mol) was suspended in THF (900ml) and triethylamine (116ml, 0.83mol) was added. The resulting white suspension was cooled to 0°C and a solution of di-*tert*-butyl dicarbonate (84.2g, 0.39mol) in THF (300ml) was added dropwise over 2h. The mixture was allowed to warm up to room temperature and stirred overnight. The solvent was removed *in vacuo*, and the residue partitioned between diethyl ether (900ml) and water (600ml). The aqueous phase was extracted with diethyl ether (2 x 450ml) and the combined organic phases washed with hydrochloric acid (500ml, 1M), sodium bicarbonate (500ml, 10% aq.) and brine (500ml). The combined organic phases were dried and concentrated *in vacuo* to give the carbamate (80g, 95%) as a colourless oil; $[\alpha]_D = +17.9$ (c = 5.0, MeOH), [Lit. +17.5 (c = 5.0, MeOH)]¹⁴³; ν_{\max} (film) 3400, 1700cm⁻¹; δ_H (500MHz) 5.63 (d, *J* 7.7, 1H, *NH*), 4.30 (br s, 1H, *CHNHBOC*), 3.91-3.85 (m, 1H, *CHHOH*), 3.82-3.75 (m, 1H, *CHHOH*), 3.71 (s, 3H, *OCH*₃), 3.43 (br s, 1H, *OH*), 1.39 (s, 9H, *C(CH*₃)₃); δ_C (67.8MHz) 171.4 (s), 155.7 (s), 80.1 (s), 62.9 (t), 55.6 (d), 52.4 (q), 28.1 (q).

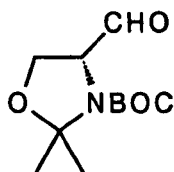
(4*R*)-2,2-Dimethyloxazolidine-3,4-dicarboxylic acid-3-*tert*-butyl ester-4-methyl ester (144)⁸⁵



Boron trifluoride diethyl etherate (3.0ml, 24mmol) was added to a solution of the carbamate (143) (80g, 0.37mol) in a mixture of acetone (900ml) and 2,2-dimethoxypropane (360ml) at room temperature. The resulting solution was stirred at room temperature for 3h until all the starting material had been consumed, as

determined by TLC. The solvent was removed *in vacuo*, the residual oil taken up in dichloromethane (900ml) and washed with a saturated solution of sodium bicarbonate (2 x 800ml, 50% aq.), then brine (800ml). The organic phase was then dried and concentrated *in vacuo* to give the oxazolidine as a yellow oil, which was purified by distillation (72.0g, 77%); b.p. 110°C/2mmHg, [lit. b.p. 101-102°C/2mmHg]⁸⁵; $[\alpha]_D = +52.5$ ($c = 1.5$, CHCl_3), [lit $[\alpha]_D = +53.0$ ($c = 1.3$, CHCl_3)]⁸⁵; ν_{max} (film) 1759, 1709 cm^{-1} ; δ_{H} (400MHz, C_6D_6 , T=346K) 4.40 (br s, 1H, CHNBOC), 3.91-3.82 (m, 2H, CH_2O), 3.41 (s, 3H, OCH_3), 1.77 (br s, 3H, CCH_3), 1.52 (br s, 3H, CCH_3), 1.41 (s, 9H, $\text{C}(\text{CH}_3)_3$); m/z (EI) Found: 244.1183 ($[\text{M-Me}]^+$ $\text{C}_{11}\text{H}_{18}\text{NO}_5$ requires 244.1185).

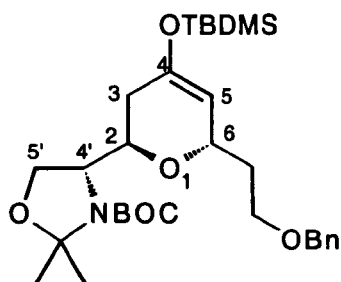
(4*R*)-4-Formyl-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (145)⁸⁵



The ester (144) (28.5g, 0.11mol) was dissolved in anhydrous toluene (250ml) and the solution cooled to -78°C before dropwise addition of a solution of diisobutylaluminium hydride (125ml, 1.5M in toluene, 0.18mol). Stirring was continued at -78°C for 3h before slow addition of anhydrous methanol (30ml) and warming to room temperature. The mixture was then poured into a solution of potassium sodium tartrate (90g) in water (250ml) and the biphasic mixture stirred for 2h, the phases were separated and the aqueous layer extracted with diethyl ether (2 x 400ml). The organic layers were combined, dried and concentrated *in vacuo* to leave the aldehyde as a yellow oil, which was purified by distillation (18.8g, 75%), b.p. 100°C/1mmHg, [lit. b.p. 101-102°C/2mmHg]⁸⁵; $[\alpha]_D = +83.0$ ($c = 1.3$, CHCl_3), [lit $[\alpha]_D = +95.0$ ($c=1.3$, CHCl_3)]⁸⁵; ν_{max} (film) 2979, 2717, 1739, 1709 cm^{-1} ; δ_{H} (400MHz, C_6D_6 , T = 346K) 9.42 (br s, 1H, CHCHO), 4.05-3.95 (br m, 1H, CHNBOC), 3.75 (dd, J 9.3, 3.5,

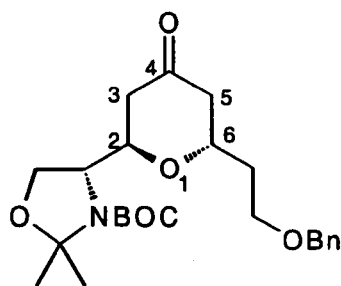
1H, CHCHHO), 3.66 (dd, J 9.3, 7.2, 1H, CHCHHO), 1.61 (s, 3H, CCH₃), 1.48 (s, 3H, CCH₃), 1.40 (s, 9H, C(CH₃)₃).

(2*R*, 6*S*, 4'*R*)-4'-[6-(2''-Benzyloxy-ethyl)-4-(*tert*-butyl-dimethyl-silanyloxy)-3,6-dihydro-2*H*-pyran-2-yl]-2',2'-dimethyl-oxazolidine-3'-carboxylic acid *tert*-butyl ester (150)



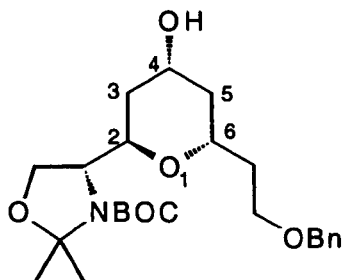
Zinc chloride (7.40g, 54.1mmol) was added in one portion to a stirred solution of the aldehyde (**145**) (12.4g, 54.1mmol) in hexane (250ml) at room temperature, under a nitrogen atmosphere. After 10min a solution of the diene (**118**) (11.5g, 36.1mmol) in hexane (50ml) was added and stirring continued at room temperature for 5 days until the diene was completely consumed, as determined by TLC. The solution was then added to saturated sodium bicarbonate (300ml) and extracted with ethyl acetate (3 x 400ml). The organic layers were combined, dried (Na₂SO₄) and the solvent removed *in vacuo* to leave a yellow oil, which was purified by chromatography eluting with 10% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *cycloadduct* (13.0g, 65%) as a colourless oil; $[\alpha]_D = +23.8$ ($c = 2.0$, CHCl₃); ν_{\max} (film) 2931, 1701, 1087cm⁻¹; δ_H (500MHz, DMSO, T = 373K) 7.38-7.22 (m, 5H, Ar), 4.92 (dd, J 3.3, 2.0, 1H, *H*-5), 4.50 (s, 2H, OCH₂Ar), 4.42-4.38 (m, 1H, *H*-2), 4.17-4.13 (m, 1H, *H*-6), 4.04-3.90 (m, 3H, *H*-4', *H*-5'), 3.66-3.54 (m, 2H, CH₂OBn), 2.23-2.14 (m, 1H, *H*-3), 1.90-1.74 (m, 3H, *H*-3, CH₂CH₂OBn), 1.55 (s, 3H, CCH₃), 1.48 (s, 3H, CCH₃), 1.46 (s, 9H, CO₂C(CH₃)₃), 0.95 (s, 9H, SiC(CH₃)₃), 0.16 (s, 6H, Si(CH₃)₂); m/z (FAB) Found: 546.3218 ([M-H]⁺ C₃₀H₄₈NO₆Si requires 546.3251); Found: C, 65.4; H, 9.1; N, 2.6%, C₃₀H₄₉NO₆Si requires C, 65.8; H, 9.0; N, 2.6%.

(2*R*, 6*S*, 4'*R*)-4'-[6-(2''-Benzyloxy-ethyl)-4-oxo-tetrahydro-pyran-2-yl]-2',2'-dimethyl-oxazolidine-3'-carboxylic acid *tert*-butyl ester (152)



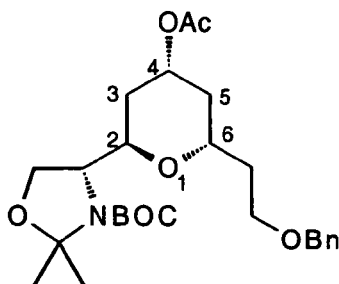
Tetrabutylammonium fluoride hydrate (4.46g, 17.1mmol) was added in one portion to a solution of the dihydropyran (**150**) (8.50g, 15.5mmol) in THF (200ml) at 0°C. The solution was stirred for 20min and then a saturated solution of ammonium chloride (200ml) was added and the solvent was removed *in vacuo*. The residue was extracted with ethyl acetate (3 x 250ml), the combined extracts were then dried (Na₂SO₄) and concentrated *in vacuo* to leave a yellow oil. The oil was purified by chromatography on silica, eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *ketone* (6.30g, 94%) as a yellow oil; $[\alpha]_D = +0.7$ ($c = 2.0$, CH₂Cl₂); ν_{\max} (film) 2978, 1699, 1392, 1366cm⁻¹; δ_H (500MHz, C₆D₆, T = 348K) 7.35-7.19 (m, 5H, Ar), 4.49-4.46 (m, 1H, *H*-2), 4.42-4.36 (m, 3H, *H*-6, OCH₂Ar), 4.12-4.06 (m, 2H, *H*-4', *H*-5'), 3.82 (dd, *J* 9.7, 6.7, 1H, *H*-5'), 3.54-3.42 (m, 2H, CH₂OBn), 2.46-2.39 (m, 3H), 2.15 (dd, *J* 14.8, 4.1, 1H), 1.92-1.75 (m, 2H, CH₂CH₂OBn), 1.51 (s, 3H, CCH₃), 1.49 (s, 3H, CCH₃), 1.47 (s, 9H, CO₂C(CH₃)₃); δ_C (125MHz, C₆D₆, T = 348K) 205.3 (s), 153.2 (s), 139.9 (s), 129.1 (d), 128.4 (d), 128.2 (d), 95.1 (s), 80.0 (s), 73.9 (t), 72.1 (d), 70.3 (d), 67.3 (t), 64.3 (t), 60.4 (d), 46.5 (t), 42.9 (t), 34.2 (t), 29.1 (q), 27.3 (q), 24.2 (q); *m/z* (FAB) Found: 434.2547 ([MH]⁺ C₂₄H₃₆NO₆ requires 434.2543).

(2*R*, 4*R*, 6*S*, 4'*R*)-4'-[6-(2''-Benzyloxy-ethyl)-4-hydroxy-tetrahydropyran-2-yl]-2',2'-dimethyl-oxazolidine-3'-carboxylic acid *tert*-butyl ester (153)



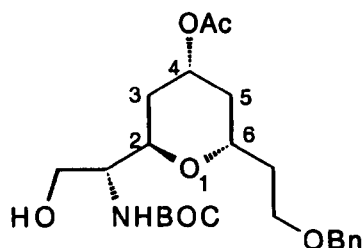
K-Selectride® (50ml, 1M in THF, 50mmol) was added dropwise over 1h to a solution of the ketone (152) (18.0g, 41.5mmol) in THF (300ml) at -78°C, under a nitrogen atmosphere. The solution was stirred for 2h and then quenched by dropwise addition of methanol (50ml) and allowing to warm to room temperature, The solvent was removed *in vacuo* and a saturated solution of ammonium chloride (100ml) was added. The residue was extracted with ethyl acetate (3 x 250ml), the combined extracts were then dried and concentrated *in vacuo* to leave colourless oil which was purified by chromatography on silica, eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C) increasing to 50% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *alcohol* (14.5g, 80%) as a colourless oil; $[\alpha]_D = -13.1$ ($c = 2.5$, CHCl_3); ν_{max} (film) 3476 (br), 1695, 1375, 1256, 1172, 1102, 1055 cm^{-1} ; δ_{H} (500MHz, $T = 334\text{K}$) major rotamer 7.33-7.25 (m, 5H, Ar), 4.50 (d, J 6.6, 2H, OCH_2Ar), 4.32-3.88 (m, 6H, $H-2$, $H-4$, $H-6$, $H-4'$, $H-5'$), 3.59-3.44 (m, 2H, CH_2OBn), 2.42-2.35 (m, 1H), 1.98-1.62 (m, 3H, $\text{CH}_2\text{CH}_2\text{OBn}$), 1.60 (s, 3H, CCH_3), 1.52 (s, 3H, CCH_3), 1.49 (s, 9H, $\text{CO}_2\text{C}(\text{CH}_3)_3$); 0.96-0.84 (m, 2H); m/z (FAB) Found: 435.2603 (M^+ $\text{C}_{24}\text{H}_{37}\text{NO}_6$ requires 435.2621).

(2*R*, 4*R*, 6*S*, 4'*R*)-4'-[4-Acetoxy-6-(2''-benzyloxy-ethyl)-tetrahydropyran-2-yl]-2',2'-dimethyl-oxazolidine-3'-carboxylic acid *tert*-butyl ester (154)



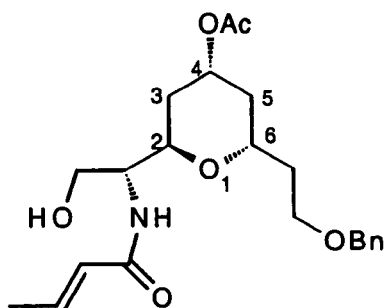
Triethylamine (1.73ml, 12.4mmol) and 4-dimethylaminopyridine (10mg, cat.) were added successively to a solution of the alcohol (153) (2.7g, 6.2mmol) in dichloromethane (100ml) at 0°C, under a nitrogen atmosphere. The solution was stirred for 5min before dropwise addition of acetic anhydride (2.34ml, 24.8mmol). The solution was stirred for 1.5h at 0°C before allowing the solution to warm to room temperature and stirring for a further 1h. A saturated solution of ammonium chloride (100ml) was added, the organic layer was separated and the aqueous phase extracted with dichloromethane (3 x 100ml). The combined organic layers were dried and the solvent removed *in vacuo*. The residue was purified by filtration through a short column of silica, eluting with 30% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *ester* (2.96g, 100%) as a yellow oil; $[\alpha]_D = -11.5$ ($c = 6.9$, CHCl_3); ν_{max} (film) 1737, 1698, 1366, 1241 cm^{-1} ; δ_{H} (500MHz, $T = 334\text{K}$) major rotamer 7.33-7.25 (m, 5H, Ar), 5.19 (br s, 1H, $H-4$), 4.50 (s, 2H, OCH_2Ar), 4.27-4.26 (m, 1H, $H-2$), 4.16-4.15 (m, 1H, $H-6$) 4.10-3.95 (m, 2H, $H-4'$, $H-5'$), 3.90 (dd, J 9.6, 6.4, 1H, $H-5'$), 3.56 (app. t, J 6.5, 2H, CH_2OBn), 2.21 (br s, 1H), 2.05-1.97 (m, 2H), 2.02 (s, 3H, OCOCH_3), 1.83-1.70 (m, 4H, CHHCH_2OBn , CCH_3), 1.61-1.51 (m, 4H, CHHCH_2OBn , CCH_3), 1.49 (s, 9H, $\text{CO}_2\text{C}(\text{CH}_3)_3$); m/z (FAB) Found: 478.2811 ($[\text{MH}]^+$ $\text{C}_{26}\text{H}_{40}\text{NO}_7$ requires 478.2805); Found: C, 65.0; H, 8.2; N, 2.4%, $\text{C}_{26}\text{H}_{39}\text{NO}_7$ requires C, 65.4; H, 8.2; N, 2.9%.

(2*R*, 4*R*, 6*S*, 1'*R*)-Acetic acid-6-(2''-benzyloxy-ethyl)-2-(1'-*tert*-butoxycarbonylamino-2'-hydroxy-ethyl)-tetrahydro-pyran-4-yl] ester
(155)



p-Toluenesulfonic acid monohydrate (2.23g, 11.7mmol) was added to a solution of the acetonide (**154**) (2.80g, 5.9mmol) in methanol (150ml) at room temperature. The solution was stirred for 1.5h, then a saturated solution of sodium bicarbonate (50ml) was added and the solvent removed *in vacuo*. The aqueous phase was extracted with ethyl acetate (3 x 150ml), the combined extracts were then dried and concentrated *in vacuo* to leave a yellow oil. The oil was purified by chromatography on silica eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *alcohol* (2.0g, 78%) as a pale yellow oil; $[\alpha]_D = -27.0$ ($c = 5.4$, CHCl_3); ν_{max} (film) 3440, 2980, 1713, 1499, 1240 cm^{-1} ; δ_{H} (360MHz) 7.36-7.25 (m, 5H, Ar), 5.19 (br s, 1H, NH), 5.15-5.11 (m, 1H, *H*-4), 4.50 (d, J 2.2, 2H, OCH_2Ar), 4.13-4.10 (m, 1H, *H*-2), 4.07-4.03 (m, 1H, *H*-6), 3.74-3.58 (m, 3H, CH_2OH , CHNH), 3.52 (t, J 6.1, 2H, CH_2OBn), 3.17 (br s, 1H, OH), 2.30-2.22 (m, 1H), 2.04 (s, 3H, OCOCH_3), 2.00-1.94 (m, 1H), 1.89-1.82 (m, 1H), 1.69-1.58 (m, 3H), 1.43 (s, 9H, $\text{C}(\text{CH}_3)_3$); δ_{C} (90MHz) 170.2 (s), 156.4 (s), 138.1 (s), 128.4 (d), 127.8 (d), 127.7 (d), 79.6 (s), 73.1 (t), 69.3 (d), 67.6 (t), 67.1 (d), 66.6 (d), 64.1 (t), 53.8 (d), 33.4 (t), 33.2 (t), 31.7 (t), 28.4 (q), 21.5 (q); m/z (EI) Found: 437.2407, (M^+ $\text{C}_{23}\text{H}_{35}\text{NO}_7$ requires 437.2414).

(2*R*, 4*R*, 6*S*, 1'*R*, *E*)-Acetic acid-6-(2'''-benzyloxy-ethyl)-2-(1'-but-2''-enoylamino-2'-hydroxy-ethyl)-tetrahydro-pyran-4-yl ester (185)

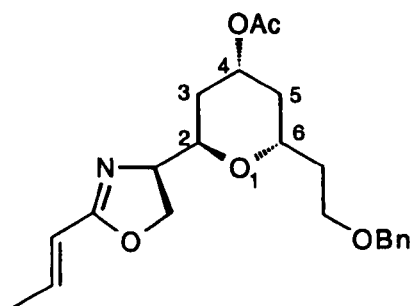


Trifluoroacetic acid (10ml, 120mmol) was added dropwise to a solution of the carbamate (**155**) (1.20g, 2.74mmol) in dichloromethane (50ml) at 0°C, under a nitrogen atmosphere. The solution was stirred for 2h, then the solvent was removed *in vacuo*. A saturated solution of sodium bicarbonate (50ml) was added to the residue and the organics were extracted with ethyl acetate (3 x 50ml), the combined extracts were then dried (Na₂SO₄) and concentrated *in vacuo* to leave the crude amine which was used immediately without purification.

Triethylamine (1.54ml, 11.0mmol) was added in one portion to a solution of the crude amine in THF (70ml) at 0°C under a nitrogen atmosphere and stirred for 15min. Crotonic acid (0.33g, 3.8mmol) was then added, followed by sequential addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.74g, 3.8mmol) and 1-hydroxybenzotriazole (0.46g, 3.4mmol). The solution was stirred at 0°C for 1h before allowing to warm to room temperature and stirring for a further 14h. Saturated ammonium chloride solution (30ml) was added and the solvent was removed *in vacuo*. The residue was extracted with ethyl acetate (4 x 50ml), the combined extracts were then dried (Na₂SO₄) and concentrated *in vacuo* to leave a yellow residue. The residue was purified by chromatography on silica, eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), increasing to 100% ethyl acetate, to give the *hydroxy-amide* (0.75g, 68%) as a colourless oil; [α]_D = -28.4 (c = 2.2, CHCl₃); ν_{\max} (soln., CHCl₃) 3658, 3428, 1731, 1681cm⁻¹; δ_{H} (500MHz) 7.37-7.30 (m, 5H, Ar), 6.85 (dq, *J* 15.1,

6.9, 1H, $\text{CH}_3\text{CH}=\text{CH}$), 6.15 (d, J 8.1, 1H, NH), 5.81 (dq, J 15.1, 1.5, 1H, $\text{CH}=\text{CHCO}$), 5.11 (tt, J 5.0, 4.1, 1H, $H-4$), 4.50 (d, J 1.3, 2H, OCH_2Ar), 4.20-4.16 (m, 1H, $H-2$), 4.07-4.02 (m, 2H, $H-6$, CHNH), 3.75-3.65 (m, 2H, CH_2OH), 3.59-3.51 (m, 2H, CH_2OBn), 3.46 (br s, 1H, OH), 2.28-2.21 (m, 1H), 2.05 (s, 3H, OCOCH_3), 1.98-1.92 (m, 1H), 1.87-1.79 (m, 1H), 1.84 (dd, J 6.9, 1.5, 3H, $\text{CH}_3\text{CH}=\text{CH}$), 1.73-1.58 (m, 3H); δ_{C} (90MHz) 170.0 (s), 166.4 (s), 140.3 (d), 138.0 (s), 128.2 (d), 127.7 (d), 127.5 (d), 124.6 (d), 72.8 (t), 68.6 (d), 67.2 (t), 66.9 (d), 66.5 (d), 63.2 (t), 52.4 (d), 33.4 (2x t), 31.5 (t), 21.2 (q), 17.5 (q); m/z (EI) Found: 405.2153, (M^+ $\text{C}_{22}\text{H}_{31}\text{NO}_6$ requires 405.2151).

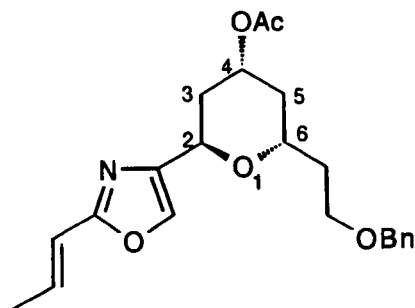
(2*R*, 4*R*, 6*S*, 4'*R*, *E*)-Acetic acid-6-(2''-benzyloxy-ethyl)-2-(2'-propenyl-4',5'-dihydro-oxazol-4'-yl)-tetrahydro-pyran-4-yl ester (186)



Diethylaminosulfur trifluoride (39 μ l, 0.30mmol) was added dropwise to a solution of the hydroxy-amide (185) (80mg, 0.20mmol) in dichloromethane (5ml) at -78°C , under a nitrogen atmosphere. The solution was stirred at -78°C for 2h and then an aqueous solution of ammonium hydroxide (4ml, 4M) and ice (10g) were added. The biphasic mixture was allowed to warm to room temperature and then extracted with dichloromethane (3 x 15ml), the combined extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to leave a yellow oil. The oil was purified by chromatography on silica, eluting with 80% ethyl acetate in petroleum ether (b.p. $40-60^\circ\text{C}$), to give the *oxazoline* (64mg, 80%) as a colourless oil; $[\alpha]_{\text{D}} = -114.0$ ($c = 2.5$, CHCl_3); ν_{max} (film) 1735, 1677 cm^{-1} ; δ_{H} (360MHz) 7.37-7.28 (m, 5H, Ar), 6.58 (dq, J 15.8, 6.9,

¹H, CH₃CH=CH), 5.99 (dq, *J* 15.8, 1.6, 1H, O_x-CH=CH), 5.30-5.22 (m, 1H, *H*-4), 4.50 (d, *J* 3.1, 2H, OCH₂Ar), 4.30-4.13 (m, 3H, CH₂O, CHN), 4.12-4.05 (m, 1H, *H*-6), 3.98 (dt, *J* 8.2, 4.0, 1H, *H*-2), 3.54 (dd, *J* 7.5, 5.9, 2H, CH₂OBn), 2.23-2.13 (m, 1H), 2.05-1.98 (m, 1H), 2.04 (s, 3H, OCOCH₃), 1.90-1.67 (m, 3H), 1.84 (dd, *J* 6.9, 1.6, 3H, CH₃CH=CH), 1.62-1.55 (m, 1H); δ_C (90MHz) 170.3 (s), 163.9 (s), 139.4 (d), 138.4 (s), 128.3 (d), 127.6 (d), 127.5 (d), 119.0 (d), 73.0 (t), 69.2 (t), 68.6 (d), 68.0 (t), 67.7 (d), 67.4 (d), 67.3 (t), 33.9 (t), 33.7 (t), 30.8 (t), 21.4 (q), 18.3 (q); *m/z* (FAB) Found: 388.2120, ([MH]⁺ C₂₂H₃₀NO₅ requires 388.2124).

(2*R*, 4*R*, 6*S*, *E*)-Acetic acid-6-(2''-benzyloxy-ethyl)-2-(2'-propenyl-oxazol-4'-yl)-tetrahydro-pyran-4-yl ester (187)

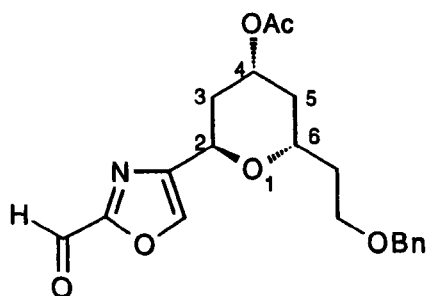


Dess-Martin periodinane (2.50g, 5.93mmol) was added in one portion to a solution of the alcohol (185) (0.80g, 1.98mmol) in dichloromethane (50ml) at room temperature, under a nitrogen atmosphere. The mixture was stirred for 3h and then diethyl ether (200ml) was added. The resulting suspension was then poured into a saturated solution of sodium thiosulfate and sodium bicarbonate (1:1, 200ml) and stirred vigorously for 30min. The organic layer was separated and the aqueous phase was extracted with diethyl ether (2 x 200ml) and the combined organic layers were dried. The solvent was removed *in vacuo* to leave a yellow waxy oil, which was used immediately without purification.

Triphenylphosphine (2.60g, 9.88mmol), followed by 2,6-di-*tert*-butylpyridine (4.40ml, 19.8mmol) and dibromotetrachloroethane (3.21g, 9.88mmol) were added to a

solution of the crude aldehyde in dichloromethane (50ml) at 0°C, under a nitrogen atmosphere. The solution was stirred for 1h and then a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (7.40ml, 49.4mmol) in acetonitrile (20ml) was added and the residual solution stirred for a further 1h. The solution was concentrated *in vacuo* to leave a dark residue which was purified by chromatography on silica, eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C) increasing to 40% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *oxazole* (0.45g, 58%) as a yellow oil; $[\alpha]_D = -54.0$ ($c = 0.3$, CHCl_3); λ_{max} (EtOH) 205 (11200), 208 (10800), 251 (9400), 258 (11200)nm; ν_{max} (film) 1798, 1242 cm^{-1} ; δ_{H} (500MHz) 7.50 (s, 1H, Ox-*H*), 7.41-7.26 (m, 5H, Ar), 6.70 (dq, J 15.9, 6.9, 1H, $\text{CH}_3\text{CH}=\text{CH}$), 6.27 (dq, J 15.9, 1.7, 1H, Ox- $\text{CH}=\text{CH}$), 5.11-5.05 (m, 2H, *H*-2, *H*-4), 4.50 (app. q, J 11.9, 2H, OCH_2Ar), 3.91-3.86 (m, 1H, *H*-6), 3.67-3.63 (m, 1H, CHHOBN), 3.59-3.55 (m, 1H, CHHOBN), 2.44-2.40 (m, 1H, *H*-3 $_{\text{ax}}$), 2.05 (s, 3H, OCOCH_3), 2.00-1.96 (m, 1H), 1.95-1.86 (m, 2H), 1.91 (dd, J 6.9, 1.7, 3H, $\text{CH}_3\text{CH}=\text{CH}$), 1.81-1.75 (m, 1H), 1.44 (ddd, J 12.2, 12.2, 10.6, 1H, *H*-5 $_{\text{ax}}$); δ_{C} (125MHz) 170.5 (s), 161.4 (s), 140.6 (s), 138.4 (s), 135.4 (d), 135.0 (d), 128.3 (d), 127.6 (d), 127.5 (d), 117.8 (d), 73.0 (t), 68.1 (d), 67.7 (d), 67.1 (d), 66.5 (t), 37.1 (t), 35.8 (t), 32.9 (t), 21.3 (q), 18.4 (q); m/z (EI) Found: 385.1882, (M^+ $\text{C}_{22}\text{H}_{27}\text{NO}_5$, requires 385.1889).

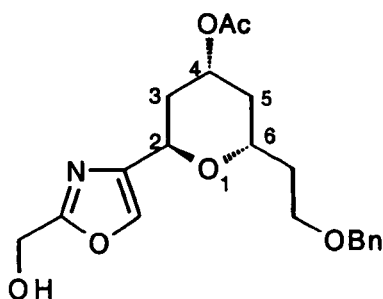
(2*R*, 4*R*, 6*S*)-Acetic acid-6-(2''-benzyloxy-ethyl)-2-(2'-formyl-oxazol-4'-yl)-tetrahydro-pyran-4-yl ester (193)



4-Methylmorpholine *N*-oxide (0.37g, 2.7mmol), followed by osmium tetroxide (20mg, cat.) were added to a solution of the oxazole (**187**) (0.35g, 0.91mmol) in acetone (30ml) and water (3ml). The solution was stirred at room temperature for 12h and then a saturated solution of sodium thiosulfate (20ml) was added. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (50ml) and the organic phase separated. The aqueous phase was extracted with ethyl acetate (3 x 50ml) and the combined organic layers were dried (Na₂SO₄). The solvent was removed *in vacuo* to leave a yellow oil, which was used immediately without purification.

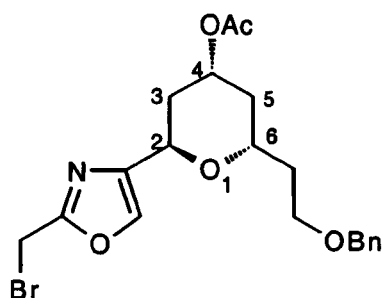
An aqueous solution of sodium periodate (0.28g, 0.65M, 1.3mmol) was added dropwise over 5min to a vigorously stirred suspension of silica (2g) in dichloromethane (20ml). The crude diol in dichloromethane (5ml) was then added dropwise over 2min and the suspension stirred for 30min. The suspension was filtered and the silica was washed with dichloromethane (2 x 75ml). The solvent was removed *in vacuo* to leave a yellow oil which was purified by chromatography on silica, eluting with 40% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *aldehyde* (0.30g, 88%) as a yellow oil; $[\alpha]_D = -54.3$ ($c = 1.1$, CHCl₃); ν_{\max} (film) 2861, 1736, 1707cm⁻¹; δ_H (360MHz) 9.67 (d, J 0.7, 1H, CHO), 7.87 (d, J 0.7, 1H, Ox-H), 7.36-7.25 (m, 5H, Ar), 5.19 (br d, J 5.2, 1H, H-2), 5.01 (m, 1H, H-4), 4.49 (s, 2H, OCH₂Ar), 3.92-3.85 (m, 1H, H-6), 3.70-3.64 (m, 1H, CHHOBn), 3.57-3.49 (m, 1H, CHHOBn), 2.53-2.47 (m, 1H, H-3_{ax}), 2.05 (s, 3H, OCOCH₃), 2.04-1.75 (m, 4H, H-3_{eq}, H-5_{eq}, CH₂CH₂OBn), 1.46 (ddd, J 12.3, 12.3, 10.5, 1H, H-5_{ax}); δ_C (90MHz) 177.0 (d), 170.1 (s), 157.8 (s), 143.3 (s), 139.6 (d), 138.0 (s), 128.2 (d), 127.5 (d), 127.4 (d), 72.8 (t), 67.7 (d), 67.1 (2x d), 65.9 (t), 36.8 (t), 35.4 (t), 32.6 (t), 21.0 (q); m/z (FAB) Found: 374.1609, ([MH]⁺ C₂₀H₂₄NO₆ requires 374.1604).

(2R, 4R, 6S)-Acetic acid-6-(2''-benzyloxy-ethyl)-2-(2'-hydroxymethyl-oxazol-4'-yl)-tetrahydro-pyran-4-yl ester (194)



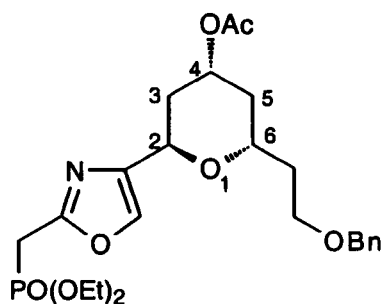
Sodium borohydride (88mg, 2.3mmol) was added in one portion to a solution of the aldehyde (193) (0.29g, 0.78mmol) in methanol (20ml) at 0°C, under a nitrogen atmosphere. The solution was stirred for 1h at 0°C and then a solution of saturated ammonium chloride (20ml) was added and the solvent removed *in vacuo*. The mixture was extracted with ethyl acetate (3 x 150ml), the combined extracts were then dried (Na₂SO₄) and concentrated *in vacuo* to leave a yellow oil. The oil was purified by chromatography on silica, eluting with 80% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *alcohol* (0.26g, 89%) as a yellow oil; $[\alpha]_D = -54.3$ (c = 1.1, CHCl₃); ν_{\max} (film) 3408, 1737, 1098cm⁻¹; δ_H (360MHz) 7.60 (d, *J* 1.4, 1H, O_x-H), 7.36-7.26 (m, 5H, Ar), 5.09 (br d, *J* 5.5, 1H, H-2), 5.06-5.02 (m, 1H, H-4), 4.64 (d, *J* 5.4, 2H, CH₂OH), 4.49 (s, 2H, OCH₂Ar), 4.36 (t, *J* 5.9, 1H, OH), 3.88-3.84 (m, 1H, H-6), 3.68-3.53 (m, 2H, CH₂OBn), 2.42 (dt, *J* 13.0, 2.2, 1H, H-3_{ax}), 2.05 (s, 3H, OCOCH₃), 2.00-1.78 (m, 4H, H-3_{eq}, H-5_{eq}, CH₂CH₂OBn), 1.44 (ddd, *J* 12.3, 12.3, 10.6, 1H, H-5_{ax}); δ_C (90MHz) 170.4 (s), 163.7 (s), 139.7 (s), 138.2 (s), 136.2 (d), 128.2 (d), 127.4 (2x d), 72.8 (t), 67.8 (d), 67.5 (d), 67.0 (d), 66.2 (t), 56.9 (t), 36.9 (t), 35.5 (t), 32.7 (t), 21.1 (q); *m/z* (EI) Found: 375.1684, (M⁺ C₂₀H₂₅NO₆ requires 375.1682).

(2*R*, 4*R*, 6*S*)-Acetic acid-6-(2''-benzyloxy-ethyl)-2-(2'-bromomethyl-oxazol-4'-yl)-tetrahydro-pyran-4-yl ester (195)



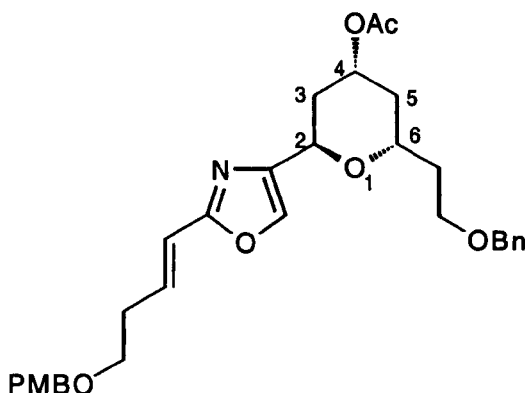
A solution of triphenylphosphine (118mg, 0.45mmol) in dichloromethane (3ml) was added dropwise to a solution of the alcohol (**194**) (130mg, 0.35mmol) and carbon tetrabromide (172mg, 0.52mmol) in dichloromethane (7ml) at 0°C, under a nitrogen atmosphere. The solution was stirred for 15h while allowing to warm to room temperature and then the solvent was removed *in vacuo*. The residue was purified by chromatography on silica, eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *bromide* (122mg, 80%) as a colourless oil; $[\alpha]_D = -42.7$ ($c = 5.5$, CHCl_3); ν_{max} (film) 1736, 1242, 1098 cm^{-1} ; δ_{H} (500MHz) 7.62 (d, J 1.4, 1H, Ox-H), 7.37-7.28 (m, 5H, Ar), 5.12 (br d, J 5.6, 1H, $H-2$), 5.06-5.02 (m, 1H, $H-4$), 4.51 (d, J 2.2, 2H, OCH_2Ar), 4.38 (s, 2H, CH_2Br), 3.89-3.85 (m, 1H, $H-6$), 3.65-3.55 (m, 2H, CH_2OBn), 2.43-2.40 (m, 1H, $H-5$), 2.05 (s, 3H, OCOCH_3), 2.01-1.78 (m, 4H), 1.45 (ddd, J 12.3, 12.3, 10.5, 1H, $H-5$); δ_{C} (90MHz) 170.3 (s), 159.4 (s), 141.0 (s), 138.3 (s), 137.3 (d), 128.3 (d), 127.5 (2x d), 72.9 (t), 67.9 (d), 67.5 (d), 67.1 (d), 66.2 (t), 37.0 (t), 35.6 (t), 32.7 (t), 21.1 (q), 20.1 (t); m/z (FAB) Found: 438.0898, ($[\text{MH}]^+ \text{C}_{20}\text{H}_{25}\text{NO}_5\text{Br}^{79}$ requires 438.0916).

(2*R*, 4*R*, 6*S*)-Acetic acid-6-(2''-benzyloxy-ethyl)-2-(2'-(diethoxyphosphorylmethyl)-oxazol-4'-yl)-tetrahydro-pyran-4-yl ester (196)



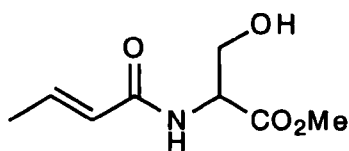
Triethyl phosphite (0.40ml, 2.3mmol) was added to a solution of the bromide (**195**) (110mg, 0.25mmol) in toluene (0.8ml) under a nitrogen atmosphere. The solution was refluxed for 3.5h, then cooled and the solvent was removed *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate, to give the *phosphonate* (118mg, 95%) as a colourless oil; $[\alpha]_D = -54.3$ ($c = 1.1$, CHCl_3); ν_{max} (film) 1737, 1244, 1097, 1027, 971 cm^{-1} ; δ_{H} (360MHz) 7.58 (t, J 1.3, 1H, Ox-*H*), 7.36-7.26 (m, 5H, Ar), 5.09 (br d, J 5.4, 1H, *H*-2), 5.06-5.02 (m, 1H, *H*-4), 4.49 (s, 2H, OCH_2Ar), 4.17-4.09 (m, 4H, $\text{P}(\text{OCH}_2\text{CH}_3)_2$), 3.90-3.84 (m, 1H, *H*-6), 3.66-3.52 (m, 2H, CH_2OBn), 3.34 (d, $J_{\text{P-H}}$ 21.4, 2H, Ox- CH_2P), 2.43-2.39 (m, 1H, *H*-3*ax*), 2.04 (s, 3H, OCOCH_3), 2.00-1.73 (m, 4H, *H*-3*eq*, *H*-5*eq*, $\text{CH}_2\text{CH}_2\text{OBn}$), 1.42 (ddd, J 12.3, 12.3, 10.6, 1H, *H*-5*ax*), 1.31 (t, J 7.1, 6H, $\text{P}(\text{OCH}_2\text{CH}_3)_2$); δ_{C} (90MHz) 170.4 (s), 156.5 (sd, $J_{\text{P-C}}$ 10.4), 140.5 (sd, $J_{\text{P-C}}$ 1.6), 138.3 (s), 136.7 (dd, $J_{\text{P-C}}$ 2.1), 128.4 (d), 128.3 (d), 127.6 (d), 73.0 (t), 68.0 (d), 67.6 (d), 67.2 (d), 66.4 (t), 62.8 (td, $J_{\text{P-C}}$ 3.7), 62.7 (td, $J_{\text{P-C}}$ 3.8), 37.0 (t), 35.7 (t), 32.9 (t), 27.5 (td, $J_{\text{P-C}}$ 140.5), 21.3 (q), 16.3 (2x q); m/z (FAB) Found: 496.2106, ($[\text{MH}]^+$ $\text{C}_{24}\text{H}_{35}\text{NO}_8\text{P}$ requires 496.2100).

(2*R*, 4*R*, 6*S*)-Acetic acid-6-(2'''-benzyloxy-ethyl)-2-{2'-[4''-(4'''-methoxy-benzyloxy)-but-1''-enyl]-oxazol-4'-yl)-tetrahydro-pyran-4-yl ester (201)



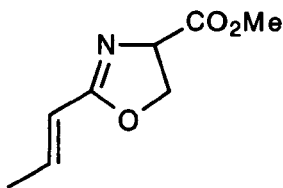
Lithium chloride (0.8mg, 19μmol) followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (2.4μl, 16μmol) were added to a solution of the phosphonate (196) (8mg, 16μmol) in acetonitrile (1ml) at room temperature, under a nitrogen atmosphere. The solution was stirred for 10min before addition of the 3-(*p*-methoxybenzyloxy)-propionaldehyde (3.2mg, 16μmol) in acetonitrile (0.5ml) and stirring was continued for a further 2h. The solvent was removed *in vacuo*, and the residue was purified by chromatography on silica, eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *olefin* (6mg, 70%) as a colourless oil; δ_{H} (500MHz) 7.51 (d, *J* 0.9, 1H, Ox-*H*), 7.35-7.26 (m, 7H, Ar), 6.89 (d, *J* 8.6, 2H, Ar), 6.71 (dt, *J* 16.1, 7.0, 1H, CH₂CH=CH), 6.33 (d, *J* 16.1, 1H, Ox-CH=CH), 5.12-5.05 (m, 2H, *H*-2, *H*-4), 4.50 (d, *J* 3.2, 2H, OCH₂Ar), 4.47 (s, 2H, OCH₂Ar), 3.91-3.87 (m, 1H, *H*-6), 3.81 (s, 3H, OCH₃), 3.67-3.55 (m, 4H, CH₂OBn, CH₂OPMB), 2.53 (app. qd, *J* 6.7, 1.0, 2H, CH=CHCH₂), 2.43 (dt, *J* 12.9, 2.2, 1H, *H*-3_{ax}), 2.05 (s, 3H, OCOCH₃), 2.01-1.78 (m, 4H, *H*-3_{eq}, *H*-5_{eq}, CH₂CH₂OBn), 1.44 (ddd, *J* 12.2, 12.2, 10.7, 1H, *H*-5_{ax}); δ_{C} (125MHz) 170.5 (s), 161.2 (s), 159.2 (s), 140.7 (s), 138.4 (s), 136.5 (d), 135.2 (d), 130.2 (s), 129.3 (d), 128.4 (d), 127.7 (d), 127.5 (d), 118.1 (d), 113.8 (d), 73.1 (t), 72.7 (t), 68.5 (t), 68.2 (d), 67.7 (d), 67.1 (d), 66.5 (t), 55.3 (q), 37.1 (t), 35.8 (t), 33.2 (t), 32.9 (t), 21.3 (q); *m/z* (FAB) Found: 536.2646, ([MH]⁺ C₃₁H₃₈NO₇ requires 536.2648).

(E)-2-But-2'-enoylamino-3-hydroxy-propionic acid methyl ester (203)



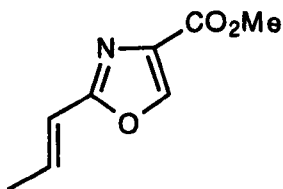
Triethylamine (7.2ml, 51.4mmol) was added to a suspension of *dl*-serine methyl ester hydrochloride (2.0g, 12.9mmol) in THF (50ml) at 0°C, under a nitrogen atmosphere. The suspension was stirred for 15min and then crotonic acid (1.0g, 11.6mmol) was added in one portion. After a further 5min, 1-hydroxybenzotriazole (2.2g, 16.1mmol) was added, followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (3.5g, 18.0mmol) and the resultant suspension was stirred for 36h at room temperature. Saturated ammonium chloride solution (20ml) was added and the solvent was removed *in vacuo*. The residue was extracted with ethyl acetate (3 x 75ml), the combined extracts were then dried and concentrated *in vacuo* to leave a yellow oil. The oil was purified by chromatography on silica, eluting with ethyl acetate, to give the *amide* (1.74g, 80%) as a colourless oil; ν_{\max} (soln., CHCl_3) 3356 (br), 1741, 1672 cm^{-1} ; δ_{H} (360MHz) 6.97 (d, J 7.8, 1H, NH), 6.81 (dq, J 15.7, 6.8, 1H, $\text{CH}=\text{CHCH}_3$), 5.92 (dq, J 15.7, 1.6, 1H, $\text{COCH}=\text{CH}$), 4.67-4.63 (m, 1H, CHCO_2CH_3), 4.05 (brs, 1H, OH), 3.94 (dd, J 11.2, 3.3, 1H, CHHOH), 3.83 (dd, J 11.2, 2.9, 1H, CHHOH), 3.72 (s, 3H, CO_2CH_3), 1.80 (dd, J 6.8, 1.6, 3H, $\text{CH}=\text{CHCH}_3$); δ_{C} (90MHz) 172.0 (s), 166.4 (s), 141.2 (d), 124.3 (d), 62.8 (t), 54.6 (d), 52.5 (q), 17.7 (q); m/z (EI) Found: 188.0932 ($[\text{MH}]^+$ $\text{C}_8\text{H}_{14}\text{NO}_4$ requires 188.0923); Found: C, 51.0; H, 7.2; N, 7.5%, $\text{C}_8\text{H}_{13}\text{NO}_4$ requires C, 51.3; H, 7.0; N, 7.5%.

(E)-2-Propenyl-4,5-dihydro-oxazole-4-carboxylic acid methyl ester (204)



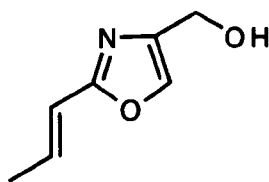
Diethylaminosulfur trifluoride (1.70ml, 12.5mmol) was added dropwise to a solution of the hydroxy-amide (**203**) (1.80g, 9.6mmol) in dichloromethane (40ml) at -78°C , under a nitrogen atmosphere. The solution was stirred at -78°C for 2h and then an aqueous solution of ammonium hydroxide (20ml, 4M) and ice (40g) were added. The biphasic mixture was allowed to warm to room temperature and then extracted with dichloromethane (3 x 50ml), the combined extracts were then dried and concentrated *in vacuo* to leave a brown oil. The oil was purified by chromatography on silica, eluting with 80% ethyl acetate in petroleum ether (b.p. $40-60^{\circ}\text{C}$), to give the *oxazoline* (1.25g, 77%) as a yellow oil; ν_{max} (film) 2954, 2914, 1742, 1675, 1609, 1208 cm^{-1} ; δ_{H} (360MHz) 6.68 (dq, J 15.8, 7.0, 1H, $\text{CH}=\text{CHCH}_3$), 6.03 (dq, J 15.8, 1.7, 1H, $\text{Ox-CH}=\text{CH}$), 4.81 (dd, J 10.5, 7.9, 1H, CHCO_2CH_3), 4.52 (dd, J 8.5, 7.9, 1H, CHHO), 4.45 (dd, J 10.5, 8.7, 1H, CHHO), 3.79 (s, 3H, CO_2CH_3), 1.88 (dd, J 7.0, 1.7, 3H, $\text{CH}=\text{CHCH}_3$); δ_{C} (67.8MHz) 171.5 (s), 165.3 (s), 140.8 (d), 118.2 (d), 68.8 (t), 68.0 (d), 52.5 (q), 18.3 (q); m/z (EI) Found: 169.0744 (M^+ $\text{C}_8\text{H}_{11}\text{NO}_3$ requires 169.0739).

(E)-2-Propenyl-oxazole-4-carboxylic acid methyl ester (205)



1,8-Diazabicyclo[5.4.0]undec-7-ene (1.2ml, 7.8mmol) was added in one portion to a solution of the oxazoline (**204**) (1.1g, 6.5mmol) in dichloromethane (20ml) at 0°C, under a nitrogen atmosphere. Bromotrichloromethane (0.77ml, 7.8mmol) was then added dropwise and the solution was stirred for 3h whilst allowing to warm to room temperature. A solution of saturated ammonium chloride (30ml) was added and the organics were extracted with dichloromethane (3 x 50ml), the combined extracts were then dried and concentrated *in vacuo* to leave a yellow residue. The residue was purified by chromatography on silica, eluting with 40% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *oxazole* (1.02g, 94%) which crystallised as a white solid; mp 42-44°C (Ben./Hex.); ν_{\max} (soln., CHCl₃) 2992, 2953, 2849, 1730, 1668, 1580, 1322, 1117, 965cm⁻¹; δ_{H} (360MHz) 8.09 (s, 1H, *H*-5), 6.80 (dq, *J* 15.9, 6.9, 1H, CH=CHCH₃), 6.28 (dq, *J* 15.9, 1.7, 1H, Ox-CH=CH), 3.86 (s, 3H, CO₂CH₃), 1.90 (dd, *J* 6.9, 1.7, 3H, CH=CHCH₃); δ_{C} (90MHz) 161.6 (s), 142.9 (s, d), 137.5 (d), 133.7 (s), 117.0 (d), 52.0 (q), 18.4 (q); *m/z* (EI) Found: 167.0586 (M⁺ C₈H₉NO₃ requires 167.0582); Found: C, 57.4; H, 5.4; N, 8.3%, C₈H₉NO₃ requires C, 57.5; H, 5.4; N, 8.4%.

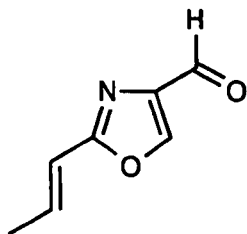
(*E*)-(2-Propenyl-oxazol-4-yl)-methanol (206**)**



A solution of di-*isobutyl*aluminium hydride (22.8ml, 1.5M in toluene, 34.3mmol) was added dropwise over 20min to a solution of the ester (**205**) (2.2g, 13.2mmol) in toluene (80ml) and dichloromethane (10ml) at -78°C, under a nitrogen atmosphere. The solution was stirred at -78°C for 2h and then at 0°C for a further 2h, before careful addition of methanol (50ml). The resultant suspension was then poured into a slurry of ethyl acetate (300ml) and magnesium sulfate and stirred vigorously for 2h. The slurry

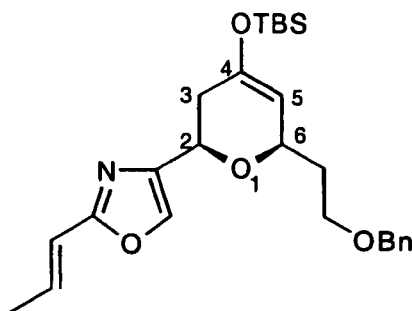
was then filtered through a pad of Celite and washed with ethyl acetate (1l) and concentrated *in vacuo* to leave the *alcohol* (1.22g, 67%) which crystallised as a white solid; m.p. 59-61°C (Hex./Et₂O); ν_{\max} (soln., CHCl₃) 3262 (br), 2974, 2878, 1667, 1350 cm⁻¹; δ_{H} (360MHz) 7.44 (s, 1H, *H*-5), 6.70 (dq, *J* 15.9, 6.9, 1H, CH=CHCH₃), 6.24 (dq, *J* 15.9, 1.7, 1H, Ox-CH=CH), 5.11 (br s, 1H, OH), 4.53 (s, 2H, CH₂OH), 1.89 (dd, *J* 6.9, 1.7, 3H, CH=CHCH₃); δ_{C} (67.8MHz) 161.6 (s), 140.9 (s), 136.1 (d), 134.2 (d), 117.3 (d), 55.7 (t), 20.2 (q); *m/z* (EI) Found: 139.0635 (M⁺ C₇H₉NO₂ requires 139.0633); Found: C, 60.1; H, 6.6; N, 9.9%, C₇H₉NO₂ requires C, 60.4; H, 6.5; N, 10.1%.

(*E*)-2-Propenyl-oxazole-4-carbaldehyde (207)



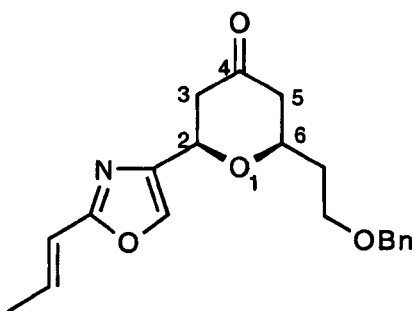
Activated manganese dioxide (1.82g, 21.0mmol) was added in one portion to a solution of the oxazole alcohol (**206**) (0.35g, 2.5mmol) in dichloromethane (40ml). The solution was stirred at room temperature for 16h until all of the starting material had been consumed. The mixture was then filtered through Celite and concentrated *in vacuo* to leave the *aldehyde* (0.28g, 80%) which crystallised as a white solid; m.p. 82°C (Hex./Et₂O); ν_{\max} (soln., CHCl₃) 2762, 1698 cm⁻¹; δ_{H} (360MHz) 9.89 (s, 1H, CHO), 8.16 (s, 1H, *H*-5), 6.85 (dq, *J* 16.0, 6.9, 1H, CH=CHCH₃), 6.31 (dq, *J* 16.0, 1.8, 1H, Ox-CH=CH), 1.94 (dd, *J* 6.9, 1.8, 3H, CH=CHCH₃); δ_{C} (90MHz) 161.6 (s), 140.9 (s), 136.1 (d), 134.2 (d), 117.3 (d), 55.7 (t), 20.2 (q); *m/z* (EI) Found: 137.0471 (M⁺ C₇H₇NO₂ requires 137.0471); Found: C, 61.3; H, 5.2; N, 10.2%, C₇H₇NO₂ requires C, 61.1; H, 5.2; N, 10.0%.

(+/-)-(2*R, 6*R**, *E*)-4'-[6-(2''-Benzyloxy-ethyl)-4-(*tert*-butyl-dimethyl-silanyloxy)-3,6-dihydro-2*H*-pyran-2-yl]-2'-propenyl-oxazole (208)**



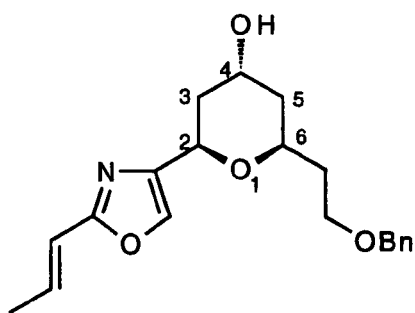
Boron trifluoride diethyl etherate (53μl, 0.43mmol) was added dropwise to a solution of the diene (118) (125mg, 0.39mmol) and the aldehyde (207) (59mg, 0.43mmol) in diethyl ether (5ml) at -78°C, under an argon atmosphere. The solution was stirred at -78°C for 2h and then a saturated solution of sodium bicarbonate (5ml) was added. The biphasic mixture was extracted with ethyl acetate (3 x 15ml), the combined extracts were then dried (Na₂SO₄) and concentrated *in vacuo* to leave a colourless oil. The oil was purified by chromatography on silica, eluting with 10% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *dihdropyran* (97mg, 54%) as a colourless oil; δ_H (360MHz) 7.45 (s, 1H, O_x-H), 7.34-7.25 (m, 5H, Ar), 6.72 (dq, *J* 15.9, 6.9, 1H, CH=CHCH₃), 6.31 (d br q, *J* 15.9, 1.6, 1H, O_x-CH=CH), 4.86 (t, *J* 1.4, 1H, *H*-5), 4.63 (ddd, *J* 10.8, 3.5, 0.9, 1H, *H*-2), 4.51 (s, 2H, OCH₂Ar), 4.51-4.49 (m, 1H, *H*-6), 3.71-3.59 (m, 2H, CH₂OBn), 2.51-2.42 (m, 1H, *H*-3), 2.27 (d app. t, *J* 16.5, 2.9, 1H, *H*-3) 1.93-1.88 (m, 5H, CH=CHCH₃, CH₂CH₂OBn), 0.93 (s, 9H, SiC(CH₃)₃), 0.16 (s, 3H, SiCH₃), 0.15 (s, 3H, SiCH₃). This compound was used immediately without further characterisation.

(+/-)-(2*R, 6*R**, *E*)-6-(2''-Benzyloxy-ethyl)-2-(2'-propenyl-oxazol-4'-yl)-tetrahydro-pyran-4-one (209)**



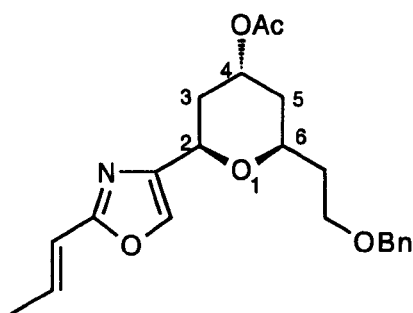
Tetrabutylammonium fluoride hydrate (85mg, 0.27mmol) was added in one portion to a solution of the dihydropyran (**208**) (95mg, 0.21mmol) in THF (5ml) at room temperature. The solution was stirred for 5min and then a saturated solution of ammonium chloride (5ml) was added and the solvent was removed *in vacuo*. The residue was extracted with ethyl acetate (3 x 15ml), and the combined extracts were then dried (Na₂SO₄) and concentrated *in vacuo* to leave a yellow oil. The oil was purified by chromatography on silica, eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *ketone* (60mg, 84%) as a colourless oil; ν_{\max} (film) 1715, 1665cm⁻¹; δ_{H} (360MHz) 7.47 (s, 1H, Ox-*H*), 7.36-7.26 (m, 5H, Ar), 6.75 (dq, *J* 15.9, 6.9, 1H, CH=CHCH₃), 6.30 (dq, *J* 15.9, 1.6, 1H, Ox-CH=CH), 4.64 (ddd, *J* 11.8, 2.8, 0.3, 1H, *H*-2), 4.50 (d, *J* 3.5, 2H, OCH₂Ar), 4.01-3.93 (m, 1H, *H*-6), 3.69-3.55 (m, 2H, CH₂OBn), 2.80 (ddd, *J* 14.7, 11.8, 0.7, 1H, *H*-3_{ax}), 2.63 (ddd, *J* 14.7, 2.8, 1.9, 1H, *H*-3_{eq}), 2.51-2.37 (m, 2H, *H*-5), 2.09-1.85 (m, 5H, CH=CHCH₃, CH₂CH₂OBn); δ_{C} (90MHz) 206.1(s), 161.6 (s), 140.7 (s), 138.3 (s), 135.8 (s), 134.2 (d), 128.4 (d), 127.6 (2x d), 117.7 (d), 74.5 (d), 73.0 (t), 71.8 (d), 66.0 (t), 47.6 (t), 46.3 (t), 36.4 (t), 18.4 (q); *m/z* (EI) Found: 341.1634, (M⁺ C₂₀H₂₃NO₄ requires 341.1627).

(+/-)-(2*R, 4*R**, 6*R**, *E*)-6-(2''-Benzyloxy-ethyl)-2-(2'-propenyl-oxazol-4'-yl)-tetrahydro-pyran-4-ol (210)**



L-Selectride® (0.21ml, 1M in THF, 0.21mmol) was added dropwise to a solution of the ketone (**209**) (50mg, 0.15mmol) in THF (4ml) at -78°C , under a nitrogen atmosphere. The solution was stirred for 30min and then a saturated solution of ammonium chloride (5ml) was added and the solvent was removed *in vacuo*. The residue was extracted with ethyl acetate (3 x 15ml), the combined extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to leave a solid residue. The residue was purified by chromatography on silica, eluting with 70% ethyl acetate in petroleum ether (b.p. $40\text{--}60^{\circ}\text{C}$), to give the *alcohol* (41mg, 82%) as a colourless oil; ν_{max} (film) 3613, 3376 (br), 1665, 1093cm^{-1} ; δ_{H} (360MHz) 7.40 (s, 1H, Ox-*H*), 7.34-7.26 (m, 5H, Ar), 6.69 (dq, J 15.9, 6.9, 1H, $\text{CH}=\text{CHCH}_3$), 6.29 (dq, J 15.9, 1.6, 1H, Ox- $\text{CH}=\text{CH}$), 4.86 (dd, J 11.2, 2.6, 1H, *H*-2), 4.51 (s, 2H, OCH_2Ar), 4.33 (br s, 1H, *H*-4), 4.16-4.11 (m, 1H, *H*-6), 3.65-3.58 (m, 2H, CH_2OBn), 2.00-1.71 (m, 8H), 1.60 (ddd, J 14.2, 11.6, 2.8, 1H, *H*-5 α); δ_{C} (90MHz) 161.2 (s), 142.7 (s), 138.5 (s), 135.1 (d), 133.9 (d), 128.3 (d), 127.6 (d), 127.4 (d), 117.9 (d), 72.8 (t), 69.4 (d), 67.3 (d), 66.8 (t), 64.2 (d), 38.3 (t), 37.7 (t), 36.2 (t), 18.4 (q); m/z (FAB) Found: 344.1872, ($[\text{MH}]^+$ $\text{C}_{20}\text{H}_{26}\text{NO}_4$ requires 344.1862).

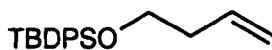
(+/-)-(2*R, 4*R**, 6*R**, *E*)-Acetic acid-6-(2''-benzyloxy-ethyl)-2-(2'-propenyl-oxazol-4'-yl)-tetrahydro-pyran-4-yl ester (211)**



Triethylamine (16μl, 0.12mmol) and 4-dimethylaminopyridine (1 crystal, cat.) were added successively to a solution of the alcohol (210) (20mg, 58μmol) at 0°C, under a nitrogen atmosphere. The solution was stirred for 5min before addition of acetic anhydride (22μl, 0.23mmol) dropwise. The solution was stirred for a further 30min at 0°C and then pipetted onto a short column of silica and eluted with 50% ethyl acetate in petroleum ether (b.p. 40-60°C) to give the *ester* (21mg, 100%) as a colourless oil; ν_{\max} (film) 1731, 1372, 1078cm⁻¹; δ_{H} (500MHz) 7.41 (s, 1H, Ox-*H*), 7.34-7.26 (m, 5H, Ar), 6.70 (dq, *J* 15.9, 6.9, 1H, CH=CHCH₃), 6.29 (dq, *J* 15.9, 1.6, 1H, Ox-CH=CH), 5.28 (t, *J* 2.8, 1H, *H*-4), 4.75 (d, *J* 11.8, 1H, *H*-2), 4.51 (s, 2H, OCH₂Ar), 4.04-4.00 (m, 1H, *H*-6), 3.67-3.55 (m, 2H, CH₂OBn), 2.11-2.08 (m, 1H), 2.10 (s, 3H, OCOCH₃) 1.93 (dd, *J* 6.9, 1.6, 3H, CH=CHCH₃), 1.91-1.75 (m, 4H), 1.62-1.58 (m, 1H); δ_{C} (90MHz) 170.3 (s), 161.3 (s), 142.4 (s), 138.5 (s), 135.3 (d), 133.9 (d), 128.3 (d), 127.6 (d), 127.5 (d), 117.9 (d), 72.9 (t), 70.0 (d), 68.2 (d), 67.4 (d), 66.4 (t), 36.1 (t), 35.4 (t), 34.8 (t), 21.3 (q), 18.4 (q); *m/z* (EI) Found: 385.1890, (M⁺ C₂₂H₂₇NO₅ requires 385.1889).

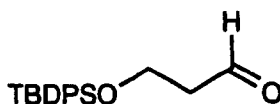
3.2 Methodology Towards *trans*-Tetrahydropyrans

But-3-enyloxy-*tert*-butyl-diphenyl-silane (230)¹⁴⁷



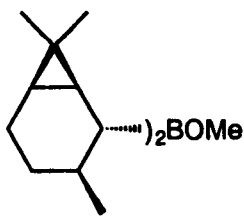
Triethylamine (19.9ml, 142mmol) and 4-dimethylaminopyridine (0.80g, 7.1mmol) were added successively in one portion to a solution of 3-buten-1-ol (5.10g, 71.1mmol) in dichloromethane (150ml) at room temperature, under a nitrogen atmosphere. The solution was stirred for 10min before dropwise addition of *tert*-butyldiphenylsilyl chloride (14.1ml, 85.3mmol) over 15min. The solution was stirred for 3h and then a saturated solution of ammonium chloride (150ml) was added. The organic phase was separated and the aqueous layer extracted with dichloromethane (3 x 100ml). The organic extracts were combined, dried and concentrated *in vacuo* to leave a yellow oil. The oil was purified by chromatography on silica, eluting with 10% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the silyl ether (19.0g, 86%) as a pale yellow oil; ν_{\max} (film) 3070, 2930, 1427, 1111cm⁻¹; δ_{H} (360MHz) 7.76-7.72 (m, 4H, Ar), 7.50-7.41(m, 6H, Ar), 5.96-5.84 (m, 1H, CH=CH₂), 5.15-5.05 (m, 2H, CH=CH₂), 3.78 (t, *J* 6.7, 2H, TBDPSOCH₂), 2.41-2.35 (m, 2H, CH₂CH=CH₂), 1.12 (s, 9H, SiC(CH₃)₃); δ_{C} (90MHz) 135.6 (d), 135.4 (d), 133.9 (s), 129.5 (d), 127.6 (d), 116.4 (t), 63.5 (t), 38.0 (t), 26.8 (q), 19.2 (s); *m/z* (EI) Found: 309.1672, ([M-H]⁺ C₂₀H₂₅OSi requires 309.1675); Found: C, 77.7; H, 8.6%, C₂₀H₂₆OSi requires C, 77.4; H, 8.4%.

3-(*tert*-Butyl-diphenyl-silanyloxy)-propionaldehyde (231)¹⁴⁷



Ozone was bubbled through a solution of but-3-enyloxy-*tert*-butyl-diphenyl-silane (**230**) (18.7g, 60mmol) in dichloromethane (500ml) at -78°C for 2h until the solution turned blue. Oxygen was then allowed to bubble through for 10min until the solution went colourless. Triphenylphosphine (19.0g, 72.5mmol) was then added in one portion and the solution was allowed to warm to room temperature over 1h. The solution was then stirred at room temperature for 12h and concentrated *in vacuo* to leave a solid residue. The residue was adsorbed onto silica gel and purified by chromatography on silica, eluting with 10% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the aldehyde (17.2g, 91%) as a colourless oil; ν_{\max} (film) 2728, 1727cm⁻¹; δ_{H} (360MHz) 9.85 (t, *J* 2.1, 1H, CHO), 7.72-7.69 (m, 4H, Ar), 7.47-7.40 (m, 6H, Ar), 4.06 (t, *J* 6.0, 2H, TBDPSOCH₂), 2.64 (td, *J* 6.0, 2.1, 2H, CH₂CHO), 1.08 (s, 9H, SiC(CH₃)₃); δ_{C} (90MHz) 201.8 (d), 135.5 (d), 133.2 (s), 129.8 (d), 127.7 (d), 58.2 (t), 46.3 (t), 26.7 (q), 19.1 (s); *m/z* (EI) Found: 255.0840, ([M-*t*Bu]⁺ C₁₅H₁₅O₂Si requires 255.0841); Found: C, 72.8; H, 7.9%, C₁₉H₂₅O₂Si requires C, 73.0; H, 7.7%.

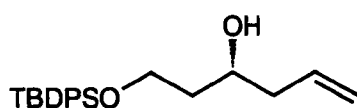
***β*-Methoxy-*bis*-(2-isocaranyl)borane (**237**)**^{116b}



Following the literature procedure described by Brown *et al.* (+)-2-carene (25.0g, 183.3mmol) (**235**) was added dropwise over 15min to a stirred solution of borane-methyl sulfide (8.6ml, 10.0M, 86.0mmol) in THF (170ml) at -10°C, under a nitrogen atmosphere. Following complete addition, stirring was discontinued and the flask containing the reaction mixture was stored at 0°C for 24h, after which time white crystalline needles of *bis*-(2-isocaranyl)borane (**236**) had separated out. The supernatant liquid was then decanted by double-ended needle, and the crystals were

washed with cooled (0°C) anhydrous diethyl ether (2 x 100ml), under a nitrogen atmosphere. The solid was then dried *in vacuo* at room temperature. *bis*-(2-Isocarnyl)borane (236) was then suspended in THF (25ml) and methanol (6.6ml) was added dropwise over 20min, at 0°C with stirring. After the evolution of hydrogen had ceased (0°C, 4h), a clear solution had formed indicating complete methanolysis. The solvent was removed *in vacuo* (15mm, 1h; 1mm, 2h) to obtain β -methoxy-*bis*-(2-isocarnyl)borane (19.1g, 73%) as a colourless oil.

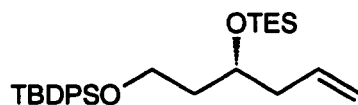
(3*R*)-1-(*tert*-Butyl-diphenyl-silanyloxy)-hex-5-en-3-ol (232)¹⁴⁸



β -Methoxy-*bis*-(2-isocarnyl)borane (237) (17.1g, 54mmol) was dissolved in anhydrous diethyl ether (80ml) and cooled to -78°C, under an argon atmosphere. Allylmagnesium bromide (51.8ml, 1.0M in Et₂O, 51.8mmol) was added dropwise over 15min to this solution at -78°C and then warmed to room temperature and stirred for 1h. The suspension was then recooled to -78°C and the aldehyde (231) (17.0g, 54mmol) was added dropwise over 30min. The suspension was then stirred at -78°C for 5h before addition of 3M sodium hydroxide (20ml) and hydrogen peroxide (40ml), and the biphasic mixture was then refluxed for 10h. The mixture was cooled and the organic layer was separated and washed with a saturated brine solution (100ml), the organic layer was dried (Na₂SO₄), and concentrated *in vacuo* to leave a colourless oil. The oil was then purified by chromatography on silica, eluting with 10% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the alcohol (13.7g, 70%) as a colourless oil; $[\alpha]_D = +4.4$ ($c = 1.5$, CHCl₃); ν_{\max} (film) 3477 (br) cm⁻¹; δ_H (360MHz) 7.71-7.68 (m, 4H, Ar), 7.48-7.39 (m, 6H, Ar), 5.92-5.81 (m, 1H, CH=CH₂), 5.15-5.10 (m, 2H, CH=CH₂) 4.01-3.92 (m, 1H, CHOH), 3.91-3.82 (m, 2H, TBDPSOCH₂), 3.26 (d, J 2.4, 1H, OH), 2.29-2.05 (m, 2H, CH₂CH=CH₂), 1.78-1.66 (m, 2H,

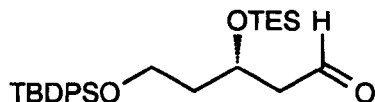
TBDPSOCH₂CH₂), 1.07 (s, 9H, SiC(CH₃)₃); δ_C (90MHz) 135.5 (d), 134.9 (d), 133.0 (s), 129.8 (d), 127.8 (d), 117.4 (t), 70.9 (d), 63.3 (t), 41.9 (t), 37.8 (t), 26.8 (q), 19.0 (s); m/z (EI) Found: 297.1310, ([M-*t*Bu]⁺ C₁₈H₂₁O₂Si requires 297.1311); Found: C, 74.6; H, 8.6%, C₂₂H₃₀O₂Si requires C, 74.5; H, 8.5%.

(4*R*)-6-(*tert*-Butyl-diphenyl-silanyloxy)-4-(triethyl-silanyloxy)-hex-1-ene (233)



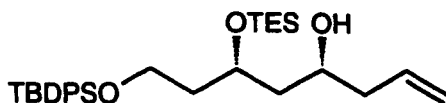
Triethylamine (1.75ml, 8.94mmol) and 4-dimethylaminopyridine (50mg, 0.45mmol) were added successively in one portion to a solution of the alcohol (232) (1.60g, 4.47mmol) in dichloromethane (50ml) at 0°C, under a nitrogen atmosphere. The solution was stirred for 10min before dropwise addition of triethylsilyl chloride (0.93ml, 5.36mmol) over 2min. The solution was stirred for 2h before addition of a saturated solution of ammonium chloride (50ml). The organic phase was separated and the aqueous layer extracted with dichloromethane (2 x 50ml). The combined organic extracts were then dried and concentrated *in vacuo* to leave a colourless oil. The oil was purified by chromatography on silica, eluting with 5% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *silyl ether* (1.83g, 88%) as a colourless oil; $[\alpha]_D = -7.2$ (c = 1.55, CHCl₃); ν_{\max} (film) 3071, 2955, 2876, 1428, 1111cm⁻¹; δ_H (360MHz) 7.70-7.66 (m, 4H, Ar), 7.46-7.36 (m, 6H, Ar), 5.88-5.77 (m, 1H, CH=CH₂), 5.06-5.01 (m, 2H, CH=CH₂), 3.98 (app. tt, *J* 6.1, 5.8, 1H, CHOTES), 3.80-3.68 (m, 2H, TBDPSOCH₂), 2.30-2.17 (m, 2H, CH₂CH=CH₂), 1.79-1.64 (m, 2H, TBDPSOCH₂CH₂), 1.07 (s, 9H, SiC(CH₃)₃), 0.95 (t, *J* 7.7, 9H, Si(CH₂CH₃)₃), 0.59 (q, *J* 7.7, 6H, Si(CH₂CH₃)₃); δ_C (90MHz) 135.6 (d), 135.1 (d), 133.9 (s), 129.5 (d), 127.6 (d), 116.8 (t), 68.8 (d), 60.7 (t), 42.1 (t), 39.7 (t), 26.8 (q), 19.2 (s), 6.9 (q), 5.0 (t); m/z (EI) Found: 411.2181, ([M-*t*Bu]⁺ C₂₄H₃₅O₂Si₂ requires 411.2176); Found: C, 71.9; H, 9.5%, C₂₈H₄₄O₂Si₂ requires C, 71.7; H, 9.5%.

(3*S*)-5-(*tert*-Butyl-diphenyl-silanyloxy)-3-(triethyl-silanyloxy)-pentanal
(234)



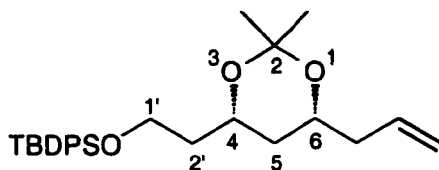
Sodium bicarbonate (3.95g, 47.0mmol) was added in one portion to a solution of the olefin (**233**) (11.0g, 23.5mmol) in dichloromethane (170ml). The solution was cooled to -78°C and ozone was bubbled through for 1h until the solution turned blue. Oxygen was then bubbled through for 10min until the solution went colourless. Triphenylphosphine (6.1g, 23.5mmol) was then added in one portion and the solution was allowed to warm to room temperature over 1h, stirred at room temperature for 12h and then a saturated solution of sodium bicarbonate (50ml) was added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 x 75ml). The combined organic extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to leave a solid residue, which was adsorbed onto silica gel and purified by chromatography on silica, eluting with 5% ethyl acetate in hexane, to give the *aldehyde* (9.3g, 84%) as a colourless oil; $[\alpha]_{\text{D}} = -2.6$ ($c = 2.4$, CH_2Cl_2); ν_{max} (film) 2730, 1730 cm^{-1} ; δ_{H} (300MHz) 9.90 (t, J 2.2, 1H, CHO), 7.70-7.66 (m, 4H, Ar), 7.45-7.36 (m, 6H, Ar), 4.40 (app. quin., J 5.9, 1H, CHOTES), 3.80-3.72 (m, 2H, TBDPSOCH₂), 2.58-2.48 (m, 2H, CH₂CHO), 1.95-1.70 (m, 2H, TBDPSOCH₂CH₂), 1.08 (s, 9H, SiC(CH₃)₃), 0.95 (t, J 8.1, 9H, Si(CH₂CH₃)₃), 0.59 (q, J 8.1, 6H, Si(CH₂CH₃)₃); δ_{C} (75MHz) 201.7 (d), 135.5 (d), 133.6 (s), 129.6 (d), 127.6 (d), 65.5 (d), 60.3 (t), 51.0 (t), 40.5 (t), 26.9 (q), 19.1 (s), 6.7 (q), 5.0 (t); m/z (FAB) Found: 471.2711, ($[\text{MH}]^+$ C₂₇H₄₃O₃Si₂ requires 471.2750).

(4*R*, 6*S*)-8-(*tert*-Butyl-diphenyl-silanyloxy)-6-(triethyl-silanyloxy)-oct-1-en-4-ol
(239)



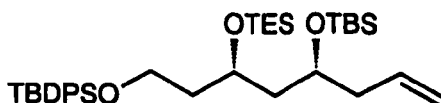
(+)- β -Methoxydiisopinocampheylborane (6.12g, 19.4mmol) was dissolved in anhydrous diethyl ether (200ml) and cooled to -78°C , under an argon atmosphere. Allylmagnesium bromide (18.6ml, 1.0M in Et_2O , 18.6mmol) was then added dropwise to this solution over 15min at -78°C and then warmed to room temperature and stirred for 1h. The suspension was then recooled to -78°C and a solution of the aldehyde (**234**) (9.10g, 19.4mmol) in diethyl ether (50ml) was added dropwise over 15mins. The suspension was then stirred at -78°C for 3h and then allowed to warm up to room temperature and stirred for a further 2h. The suspension was quenched with methanol and a solution of 3M sodium hydroxide (20ml) and hydrogen peroxide (30ml) were added and the biphasic mixture refluxed for 4h. The mixture was then cooled and the organic layer was separated and washed with a saturated brine solution (100ml), the organic layer was then dried (Na_2SO_4) and concentrated *in vacuo* to leave a colourless oil. The oil was then purified by chromatography on silica, eluting with 5% ethyl acetate in hexane, to give the *alcohol* (7.0g, 71%) as a colourless oil; $[\alpha]_{\text{D}} = +14.1$ ($c = 0.9$, CH_2Cl_2); ν_{max} (film) 3500 (br) cm^{-1} ; δ_{H} (400MHz) 7.65-7.61 (m, 4H, Ar), 7.43-7.33 (m, 6H, Ar), 5.86-5.75 (m, 1H, $\text{CH}=\text{CH}_2$), 5.10-5.05 (m, 2H, $\text{CH}=\text{CH}_2$), 4.16-4.10 (m, 1H, CHOTES), 3.81-3.73 (m, 1H, CHOH), 3.72-3.62 (m, 2H, TBDPSOCH_2), 3.28 (d, J 1.2, 1H, OH), 2.17 (app. t, J 6.1, 2H, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.92-1.78 (m, 1H, CH_2CHOH), 1.72-1.60 (m, 2H, $\text{TBDPSOCH}_2\text{CH}_2$, CH_2CHOH), 1.50-1.40 (m, 1H, $\text{TBDPSOCH}_2\text{CH}_2$), 1.03 (s, 9H, $\text{Si}(\text{CH}_3)_3$), 0.93 (t, J 8.0, 9H, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.60 (q, J 8.0, 6H, $\text{Si}(\text{CH}_2\text{CH}_3)_3$); δ_{C} (90MHz) 135.5 (d), 134.9 (d), 133.6 (s), 129.6 (d), 127.6 (d), 117.3 (t), 70.8 (d), 70.4 (d), 60.4 (t), 42.4 (t), 42.2 (t), 40.8 (t), 26.8 (q), 19.1 (s), 6.8 (q), 5.1 (t); m/z (FAB) Found: 513.3209, ($[\text{MH}]^+$ $\text{C}_{30}\text{H}_{49}\text{O}_3\text{Si}_2$ requires 513.3220); Found: C, 70.3; H, 9.5%, $\text{C}_{30}\text{H}_{48}\text{O}_3\text{Si}_2$ requires C, 70.3; H, 9.4%.

(4*S*, 6*R*)-[2'-(6-Allyl-2,2-dimethyl-[1,3]-dioxan-4-yl)-ethoxy]-*tert*-butyl-diphenyl-silane (244)



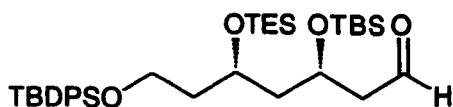
p-Toluenesulfonic acid monohydrate (4mg, 20 μ mol) was added to a solution of the alcohol (**239**) (108mg, 0.21mmol) in 2,2-dimethoxypropane (5ml) at 0°C, under a nitrogen atmosphere. The solution was stirred for 1h and the solvent was then removed *in vacuo*. The residue was purified by chromatography on silica, eluting with 5% ethyl acetate in hexane, to give the *acetone* (70mg, 76%) as a pale yellow oil; $[\alpha]_D = -1.2$ ($c = 2.7$, CHCl_3); ν_{max} (film) 3071, 2991, 2932, 2857, 1428, 1112 cm^{-1} ; δ_{H} (400MHz) 7.68-7.63 (m, 4H, Ar), 7.42-7.33 (m, 6H, Ar), 5.84-5.73 (m, 1H, $\text{CH}=\text{CH}_2$), 5.09-5.02 (m, 2H, $\text{CH}=\text{CH}_2$), 4.12-4.06 (m, 1H, CHO), 3.88-3.79 (m, 2H, CHO, TBDPSOCHH), 3.71-3.65 (m, 1H, TBDPSOCHH), 2.32-2.25 (m, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$), 2.15-2.08 (m, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.70-1.63 (m, 2H, TBDPSOCH $_2$ CH $_2$), 1.47 (ddd, J 12.9, 2.4, 2.4, 1H, CHOCHHCHO), 1.42 (s, 3H, CCH_3), 1.37 (s, 3H, CCH_3), 1.13 (ddd, J 12.7, 11.7, 11.7, 1H, CHOCHHCHO), 1.03 (s, 9H, $\text{SiC}(\text{CH}_3)_3$); δ_{C} (90MHz) 135.5 (d), 134.2 (d), 133.9 (s), 129.5 (d), 127.6 (d), 117.0 (t), 98.4 (s), 68.7 (d), 65.6 (d), 59.6 (t), 40.9 (t), 39.3 (t), 36.7 (t), 30.3 (q), 26.8 (q), 19.9 (s), 19.2 (q); m/z (FAB) Found: 439.2625, ($[\text{MH}]^+$ $\text{C}_{27}\text{H}_{39}\text{O}_3\text{Si}$ requires 439.2668).

(4*R*, 6*S*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-8-(*tert*-butyl-diphenyl-silanyloxy)-6-(triethyl-silanyloxy)-oct-1-ene (240)



Triethylamine (1.65ml, 11.7mmol) was added in one portion to a solution of the alcohol (**239**) (2.00g, 3.20mmol) in dichloromethane (50ml) at 0°C, under a nitrogen atmosphere. The solution was stirred for 5min before *tert*-butyldimethylsilyl triflate (1.17ml, 5.10mmol) was added dropwise over 1min. The solution was stirred for a further 90min at 0°C, and then a saturated solution of ammonium chloride (50ml) was added and the organic layer was separated. The aqueous fraction was then extracted with dichloromethane (2 x 100ml), the combined organic layers were then dried and concentrated *in vacuo* to leave a yellow oil. The oil was purified by chromatography on silica eluting with 5% ethyl acetate in hexane, to give the *silyl ether* (1.94g, 79%) as a colourless oil; $[\alpha]_D = -6.2$ ($c = 1.6$, CH_2Cl_2); ν_{max} (soln., CHCl_3) 2953, 2858, 1462, 1389, 1362, 1206, 1066 cm^{-1} ; δ_{H} (500MHz) 7.70-7.67 (m, 4H, Ar), 7.45-7.37 (m, 6H, Ar), 5.86-5.78 (m, 1H, $\text{CH}=\text{CH}_2$), 5.05-5.02 (m, 2H, $\text{CH}=\text{CH}_2$), 3.99-3.94 (m, 1H, CHOTES), 3.89-3.81 (m, 1H, CHOTBS), 3.78-3.70 (m, 2H, TBDPSOCH₂), 2.32-2.27 (m, 1H, $\text{CHHCH}=\text{CH}_2$), 2.22-2.15 (m, 1H, $\text{CHHCH}=\text{CH}_2$), 1.82-1.70 (m, 2H, TBDPSOCH₂CH₂), 1.63 (app. t, J 6.3, 2H, CH_2CHOTBS), 1.07 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 0.93 (m, 9H, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.90 (s, 9H, $\text{C}(\text{CH}_3)_3$), 0.61-0.54 (m, 6H, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.07 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3); δ_{C} (125MHz) 135.5 (d), 135.0 (d), 133.9 (s), 129.5 (d), 127.6 (d), 116.9 (t), 69.1 (d), 66.8 (d), 60.9 (t), 44.9 (t), 41.9 (t), 40.2 (t), 26.9 (q), 25.9 (q), 19.1 (s), 18.0 (s), 6.8 (q), 5.1 (t), -4.3 (q), -4.5 (q); m/z (EI) Found: 569.3318, $([\text{M}-t\text{Bu}]^+ \text{C}_{32}\text{H}_{33}\text{O}_3\text{Si}_3 \text{ requires } 569.3303)$.

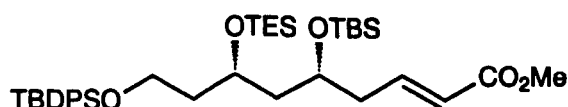
(3*S*, 5*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-7-(*tert*-butyl-diphenyl-silanyloxy)-5-(triethyl-silanyloxy)-heptanal (241**)**



Sodium bicarbonate (0.52g, 6.20mmol) was added in one portion to a solution of the olefin (**240**) (1.94g, 3.10mmol) in dichloromethane (50ml). The solution was cooled

to -78°C and ozone was bubbled through for 1h until the solution turned blue. Oxygen was then bubbled through the solution for 10min until the solution went colourless. Triphenylphosphine (0.89g, 3.41mmol) was then added in one portion and the solution was allowed to warm to room temperature over 1h, stirred at room temperature for 3h and then filtered through a pad of celite. The solvent was removed *in vacuo* to leave a solid residue which was purified by chromatography on silica, eluting with 5% ethyl acetate in hexane, to give the *aldehyde* (1.70g, 89%) as a colourless oil; $[\alpha]_{\text{D}} = +4.8$ ($c = 1.2$, CH_2Cl_2); ν_{max} (film) 2713, 1727cm^{-1} ; δ_{H} (360MHz) 9.82 (dd, J 2.9, 2.0, 1H, CHO), 7.71-7.68 (m, 4H, Ar), 7.47-7.35 (m, 6H, Ar), 4.39-4.35 (m, 1H, CHOTES), 4.01-3.96 (m, 1H, CHOTBS), 3.75 (t, J 6.6, 2H, TBDPSOCH₂), 2.65-2.59 (m, 1H, CHHCHO), 2.53-2.47 (m, 1H, CHHCHO), 1.83-1.70 (m, 4H, TBDPSOCH₂CH₂, CH₂CHOTBS), 1.09 (s, 9H, SiC(CH₃)₃), 0.96 (t, J 8.0, 9H, Si(CH₂CH₃)₃), 0.89 (s, 9H, SiC(CH₃)₃), 0.59 (q, J 8.0, 6H, Si(CH₂CH₃)₃), 0.09 (s, 6H, Si(CH₃)₂); δ_{C} (125MHz) 202.1 (d), 135.5 (d), 133.7 (s), 129.6 (d), 127.6 (d), 66.6 (d), 65.6 (d), 60.6 (t), 50.7 (t), 45.2 (t), 40.2 (t), 26.8 (q), 25.7 (q), 19.1 (s), 17.9 (s), 6.9 (q), 5.1 (t), -4.4 (q), -4.7 (q).

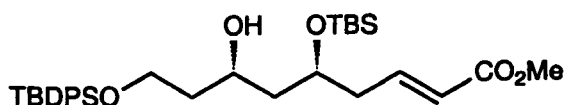
(5*R*, 7*S*, *E*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-9-(*tert*-butyl-diphenyl-silanyloxy)-7-(triethyl-silanyloxy)-non-2-enoic acid methyl ester (242)



Methyl (triphenylphosphoranylidene)acetate (0.96g, 2.86mmol) was added in one portion to a stirred solution of the aldehyde (241) (1.50g, 2.39mmol) in dichloromethane (30ml) at room temperature, under a nitrogen atmosphere. The solution was stirred at room temperature for 64h and then concentrated *in vacuo* to leave a yellow residue. The residue was purified by chromatography on silica, eluting with 10% ethyl acetate in hexane, to give the *ester* (1.56g, 95%) as a colourless oil;

$[\alpha]_D = -4.4$ ($c = 1.2$, CH_2Cl_2); ν_{max} (film) 1728cm^{-1} ; δ_{H} (360MHz) 7.70-7.67 (m, 4H, Ar), 7.46-7.37 (m, 6H, Ar), 7.00 (dt, J 15.6, 7.3, 1H, H -3), 5.86 (d, J 15.6, 1H, H -2), 3.98-3.93 (m, 2H, H -5, H -7), 3.75 (s, 3H, CO_2CH_3), 3.74-3.69 (m, 2H, H -9), 2.47-2.42 (m, 1H, H -4), 2.31-2.28 (m, 1H, H -4), 1.76 (app. q, J 6.3, 2H, CH_2), 1.70-1.62 (m, 2H, CH_2), 1.08 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 0.94 (t, J 8.0, 9H, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.89 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 0.61-0.55 (m, 6H, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.06 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3); δ_{C} (90MHz) 166.7 (s), 146.1 (d), 135.5 (d), 133.8 (s), 129.6 (d), 127.6 (d), 123.0 (d), 68.4 (d), 66.6 (d), 60.7 (t), 51.3 (q), 45.1 (t), 40.3 (t), 40.1 (t), 26.8 (q), 25.8 (q), 19.1 (s), 18.0 (s), 6.9 (q), 5.1 (t), -4.5 (2x q); m/z (FAB) Found: 627.3345, ($[\text{M}-t\text{Bu}]^+$ $\text{C}_{34}\text{H}_{55}\text{O}_5\text{Si}_3$ requires 627.3357); Found: C, 66.7; H, 9.5%, $\text{C}_{38}\text{H}_{64}\text{O}_5\text{Si}_3$ requires C, 66.6; H, 9.4%.

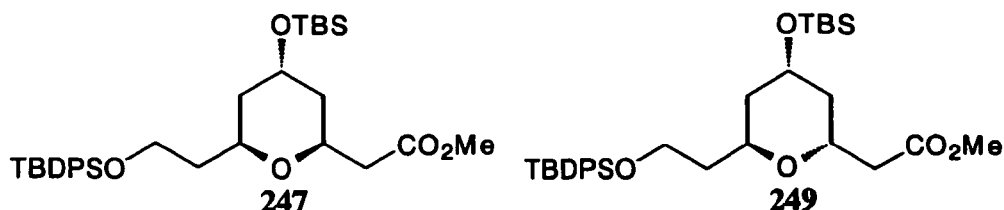
(5*R*, 7*S*, *E*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-9-(*tert*-butyl-diphenyl-silanyloxy)-7-hydroxy-non-2-enoic acid methyl ester (243)



Trifluoroacetic acid (0.35ml, 4.56mmol) was added to a solution of the ester (242) (1.20g, 1.75mmol) in THF (25ml) and water (4ml) at room temperature. The solution was stirred at room temperature for 2h before being neutralised with a saturated solution of sodium bicarbonate (20ml). The mixture was extracted with ethyl acetate (3 x 50ml), the combined extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to leave a colourless oil. The oil was purified by chromatography on silica, eluting with 10% ethyl acetate in hexane, to give the *alcohol* (0.57g, 81% based on recovered starting material) as a colourless oil; $[\alpha]_D = -3.8$ ($c = 1.3$, CH_2Cl_2); ν_{max} (film) 3526 (br) cm^{-1} ; δ_{H} (360MHz) 7.70-7.67 (m, 4H, Ar), 7.47-7.38 (m, 6H, Ar), 6.99 (dt, J 15.7, 7.7, 1H, H -3), 5.87 (d, J 15.7, 1H, H -2), 4.10-3.97 (m, 2H, H -5, H -7), 3.91-3.78 (m, 2H, H -9), 3.74 (s, 3H, CO_2CH_3), 3.43 (d, J 1.7, 1H, OH), 2.49-2.35 (m,

2H, *H*-4), 1.76-1.65 (m, 3H, *H*-6, *H*-8), 1.57 (ddd, *J* 14.0, 6.0, 3.5, 1H, *H*-6), 1.06 (s, 9H, SiC(CH₃)₃), 0.91 (s, 9H, SiC(CH₃)₃), 0.10 (s, 6H, Si(CH₃)₂); δ_C (90MHz) 166.7 (s), 145.5 (d), 135.5 (d), 133.2 (s), 129.8 (d), 127.7 (d), 123.3 (d), 70.0 (d), 68.7 (d), 62.5 (t), 51.4 (q), 44.0 (t), 40.1 (t), 39.1 (t), 26.8 (q), 25.8 (q), 19.0 (s), 18.9 (s), -4.4 (q), -4.6 (q); *m/z* (FAB) Found: 571.3342, ([MH]⁺ C₃₂H₅₁O₅Si₂ requires 517.3275); Found: C, 67.6; H, 9.1%, C₃₂H₅₀O₅Si₂ requires C, 67.3; H, 8.8%.

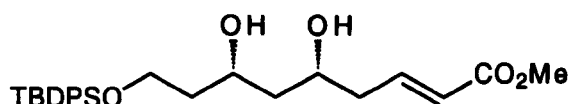
(2*S*/*R*, 4*S*, 6*S*)-{4-(*tert*-Butyl-dimethyl-silanyloxy)-6-[2'-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid methyl ester (247/249)



A solution of lithium *bis*(trimethylsilyl)amide (81 μ l, 1M in THF, 81 μ mol) was added dropwise to a solution of the alcohol (**243**) (31mg, 54 μ mol) in THF (2ml) at -78°C, under a nitrogen atmosphere. The solution was stirred at -78°C for 3h before addition of a saturated solution of ammonium chloride (2ml) and allowing to warm to room temperature. The mixture was then extracted with ethyl acetate (3 x 15ml), the combined extracts were then dried (Na₂SO₄) and the solvent removed *in vacuo* to leave a yellow oil. The oil was purified by chromatography on silica, eluting with 5% ethyl acetate in hexane, to give the *pyran* (21mg, 68%, 8:1 *cis:trans*) as a colourless oil; *cis* isomer (**247**): $[\alpha]_D = -3.9$ (c = 1.8, CH₃Cl); ν_{\max} (soln., CHCl₃) 2928, 2856, 1732, 1106, 1062cm⁻¹; δ_H (360MHz) 7.70-7.66 (m, 4H, Ar), 7.45-7.35 (m, 6H, Ar), 4.25-4.18 (m, 2H, *H*-2, *H*-4), 4.12-4.06 (m, 1H, *H*-6), 3.83-3.70 (m, 2H, CH₂OTBDPS), 3.60 (s, 3H, CO₂CH₃), 2.49 (dd, *J* 14.6, 7.4, 1H, CHHCO₂Me), 2.34 (dd, *J* 14.6, 6.4, 1H, CHHCO₂Me), 1.74-1.54 (m, 4H, 2x CH₂), 1.44-1.37 (m, 2H, CH₂), 1.05

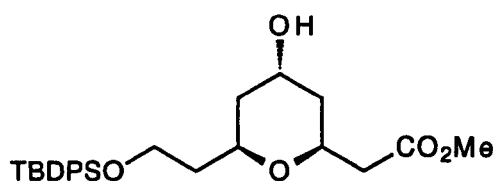
(s, 9H, SiC(CH₃)₃), 0.91 (s, 9H, SiC(CH₃)₃), 0.06 (2x s, 6H, Si(CH₃)₂); δ_C (90MHz) 171.6 (s), 135.6 (d), 134.1 (s), 129.4 (d), 127.6 (d), 68.6 (2x d), 64.9 (d), 60.3 (t), 51.4 (q), 41.4 (t), 39.4 (t), 39.1 (t), 29.7 (t), 26.8 (q), 25.8 (q), 19.2 (s), 18.0 (s), -4.4 (q); m/z (FAB) Found: 513.2523, ([M-*t*Bu]⁺ C₂₈H₄₁O₅Si₂ requires 513.2493).

(5*R*, 7*S*, *E*)-9-(*tert*-Butyl-diphenyl-silanyloxy)-5,7-dihydroxy-non-2-enoic acid methyl ester (245)



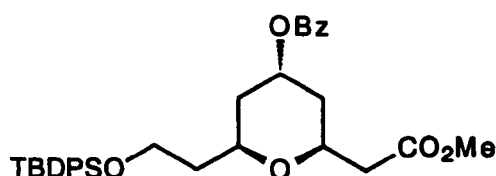
Trifluoroacetic acid (36 μ l, 0.48mmol) was added dropwise to a solution of the silyl ether (243) (89mg, 0.16mmol) in THF (10ml) and water (2ml) at 0°C. The solution was stirred at this temperature for 1h before allowing to warm to room temperature and stirring for 8h. A solution of saturated sodium bicarbonate (10ml) was then added and the solvent was removed *in vacuo*. The residue was extracted with ethyl acetate (3 x 20ml), the combined extracts were then dried (Na₂SO₄) and concentrated *in vacuo* to leave a colourless oil. The oil was purified by chromatography on silica, eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *diol* (50mg, 70%) as a colourless oil; $[\alpha]_D = +7.0$ (c = 2.2, CHCl₃); ν_{\max} (soln., CHCl₃) 3472 (br), 1715, 1660, 1106cm⁻¹; δ_H (360MHz) 7.69-7.66 (m, 4H, Ar), 7.49-7.39 (m, 6H, Ar), 7.02 (dt, *J* 15.7, 7.4, 1H, *H*-3), 5.92 (dt, *J* 15.7, 1.4, 1H, *H*-2), 4.21-4.05 (m, 4H, *H*-5, *H*-7, 2x OH), 3.89-3.86 (m, 2H, *H*-9), 3.73 (s, 3H, CO₂CH₃), 2.46-2.35 (m, 2H, *H*-4), 1.82-1.51 (m, 4H, *H*-6, *H*-8), 1.06 (s, 9H, SiC(CH₃)₃); δ_C (90MHz) 166.8 (s), 145.5 (d), 135.5 (d), 132.6 (s), 130.0 (d), 127.8 (d), 123.2 (d), 73.3 (d), 71.0 (d), 63.4 (t), 51.4 (q), 42.5 (t), 40.3 (t), 38.5 (t), 26.7 (q), 19.0 (s); m/z (FAB) Found: 457.2448, ([MH]⁺ C₂₆H₃₇O₅Si requires 457.2410).

(2*S*, 4*S*, 6*S*)-{6-[2'-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-4-hydroxy-tetrahydro-pyran-2-yl}-acetic acid methyl ester (248)



Sodium hydride (12.3mg, 60% in oil, 0.31mmol) was added in one portion to a solution of the diol (**245**) (70mg, 0.15mmol) in THF (5ml) at room temperature, under a nitrogen atmosphere. The solution was stirred for 1h and then a saturated solution of ammonium chloride (5ml) was added. The mixture was then extracted with ethyl acetate (3 x 15ml), the combined extracts were then dried (Na_2SO_4), and the solvent removed *in vacuo* to leave a colourless oil. The oil was purified by chromatography on silica eluting with 50% ethyl acetate in hexane, to give the *tetrahydropyran* (31mg, 44%) as a colourless oil; $[\alpha]_{\text{D}} = -3.9$ ($c = 0.5$, CHCl_3); ν_{max} (film) 3612, 3470 (br), 1731, 1111 cm^{-1} ; δ_{H} (400MHz) 7.69-7.66 (m, 4H, Ar), 7.44-7.36 (m, 6H, Ar), 4.24-4.17 (m, 2H, *H*-2, *H*-4), 4.02-3.97 (m, 1H, *H*-6), 3.81-3.74 (m, 2H, CH_2OTBDPS), 3.61 (s, 3H, CO_2CH_3), 2.51 (dd, J 14.9, 12.3, 1H, CHHCO_2Me), 2.36 (dd, J 14.9, 6.3, 1H, CHHCO_2Me), 1.79-1.43 (m, 6H, 3x CH_2), 1.06 (s, 9H, $\text{SiC}(\text{CH}_3)_3$); δ_{C} (75MHz) 171.5 (s), 135.5 (d), 134.0 (s), 129.4 (d), 127.5 (d), 68.7 (d), 68.4 (d), 64.4 (d), 60.4 (t), 51.1 (q), 41.2 (t), 39.0 (t), 38.4 (t), 38.2 (t), 26.6 (q), 19.2 (s); m/z (FAB) Found: 457.2444, ($[\text{MH}]^+$ $\text{C}_{26}\text{H}_{37}\text{O}_5\text{Si}$ requires 457.2410).

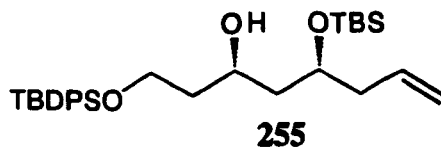
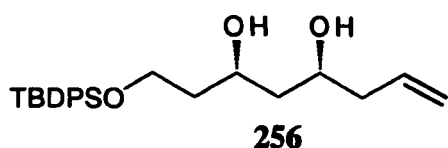
(2*S*, 4*S*, 6*S*)-Benzoic acid 2-[2'-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-6-methoxycarbonylmethyl-tetrahydro-pyran-4-yl ester (250)



Benzoyl chloride (12 μ l, 0.11mmol) and 4-dimethylaminopyridine (1mg, cat.) were added succesively to a solution of the alcohol (**248**) (30mg, 66 μ mol) in dichloromethane (2ml) at 0°C, under a nitrogen atmosphere. The solution was stirred for 10min before dropwise addition of triethylamine (18 μ l, 0.13mmol) and the solution stirred for a further 17h. The solvent was then removed *in vacuo* and the residue was purified by chromatography on silica, eluting with 20% ethyl acetate in hexane, to give the *ester* (37mg, 100%) as a colourless oil; $[\alpha]_D = -9.3$ ($c = 1.2$, CHCl_3); ν_{max} (film) 3070, 1739, 1716 cm^{-1} ; δ_{H} (360MHz) 8.14-8.12 (m, 2H, Ar), 7.72-7.67 (m, 4H, Ar), 7.64-7.60 (m, 1H, Ar), 7.50-7.31 (m, 8H, Ar), 5.52 (app. t, J 3.0, 1H, *H*-4), 4.32-4.27 (m, 1H, *H*-2), 4.20-4.16 (m, 1H, *H*-6), 3.88-3.76 (m, 2H, CH_2OTBDPS), 3.66 (s, 3H, CO_2CH_3), 2.58 (dd, J 15.0, 7.8, 1H, CHHCO_2Me), 2.45 (dd, J 15.0, 5.5, 1H, CHHCO_2Me), 2.04 (br. d, J 14.1, 1H, *H*-3), 1.97 (br d, J 14.2, 1H, *H*-5), 1.85-1.61 (m, 4H, 2x CH_2), 1.07 (s, 9H, $\text{SiC}(\text{CH}_3)_3$); δ_{C} (90MHz) 171.4 (s), 165.6 (s), 135.5 (d), 133.9 (s), 133.0 (d), 130.4 (s), 129.6 (d), 129.5 (d), 128.4 (d), 127.6 (d), 69.5 (d), 69.4 (d), 68.2 (d), 60.0 (t), 51.6 (q), 41.2 (t), 38.8 (t), 35.5 (t), 35.4 (t), 26.8 (q), 19.2 (s); m/z (FAB) Found: 561.2707, ($[\text{MH}]^+$ $\text{C}_{33}\text{H}_{41}\text{O}_6\text{Si}$ requires 561.2672).

(3*S*, 5*R*)-1-(*tert*-Butyl-diphenyl-silanyloxy)-oct-7-ene-3,5-diol (256)

(3*S*, 5*R*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-1-(*tert*-butyl-diphenyl-silanyloxy)-oct-7-ene-3,5-diol (255)



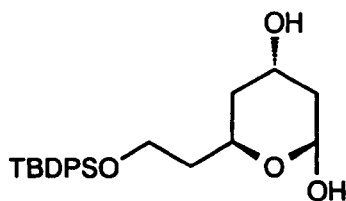
Trifluoroacetic acid (0.10ml, 1.3mmol) was added dropwise to a solution of the *tris*-silyl ether (**240**) (0.32g, 0.51mmol) in THF (15ml) and water (3ml) at 0°C. The solution was stirred at this temperature for 2h before addition of a saturated solution of sodium bicarbonate (10ml). The biphasic mixture was extracted with ethyl acetate (3 x

40ml), the combined extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to leave a colourless oil. The oil was purified by chromatography on silica, eluting with 10% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *diol* (**256**) (86mg, 42%) as a colourless oil, and the *alcohol* (**255**) (149mg, 57%) as a colourless oil. Diol (**256**); $[\alpha]_{\text{D}} = +3.8$ ($c = 0.9$, CHCl_3); ν_{max} (soln., CHCl_3) 3475cm^{-1} ; δ_{H} (360MHz) 7.71-7.67 (m, 4H, Ar), 7.49-7.39 (m, 6H, Ar), 5.92-5.80 (m, 1H, $\text{CH}=\text{CH}_2$), 5.16-5.10 (m, 2H, $\text{CH}=\text{CH}_2$), 4.20-4.14 (m, 1H, $H-3$), 4.00-3.83 (m, 4H, $H-1$, $H-5$, OH), 3.67 (br s, 1H, OH), 2.31-2.22 (m, 2H, $H-6$), 1.84-1.61 (m, 4H, $H-2$, $H-4$), 1.07 (s, 9H, $\text{SiC}(\text{CH}_3)_3$); δ_{C} (125MHz) 135.5 (d), 134.8 (d), 132.9 (s), 127.8 (d), 124.9 (d), 117.6 (t), 72.8 (d), 71.5 (d), 63.1 (t), 42.6 (t), 42.2 (t), 38.8 (t), 26.8 (q), 19.0 (s); m/z (EI) Found: 341.1575, ($[\text{M}-t\text{Bu}]^+ \text{C}_{20}\text{H}_{25}\text{O}_3\text{Si}$ requires 341.1573).

Alcohol (**255**); $[\alpha]_{\text{D}} = -10.9$ ($c = 5.1$, CH_3Cl); ν_{max} (soln., CHCl_3) 3501cm^{-1} ; δ_{H} (360MHz) 7.72-7.68 (m, 4H, Ar), 7.47-7.38 (m, 6H, Ar), 5.87-5.76 (m, 1H, $\text{CH}=\text{CH}_2$), 5.09-5.05 (m, 2H, $\text{CH}=\text{CH}_2$), 4.07-3.94 (m, 2H, $H-3$, $H-5$), 3.91-3.78 (m, 2H, $H-1$), 3.51 (d, J 1.8, 1H, OH), 2.37-2.23 (m, 2H, $H-6$), 1.78-1.58 (m, 4H, $H-2$, $H-4$), 1.06 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 0.92 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 0.11 (s, 6H, $\text{Si}(\text{CH}_3)_2$); δ_{C} (90MHz) 135.5 (d), 134.4 (d), 133.4 (s), 129.7 (d), 127.7 (d), 117.3 (t), 71.4 (d), 68.8 (d), 62.1 (t), 43.3 (t), 42.2 (t), 39.3 (t), 26.8 (q), 25.8 (q), 19.1 (s), 17.9 (s), -4.1 (q), -4.7 (q); m/z (EI) Found: 455.2455, ($[\text{M}-t\text{Bu}]^+ \text{C}_{26}\text{H}_{39}\text{O}_3\text{Si}_2$ requires 455.2448). The alcohol (**255**) could be converted to the diol (**256**) by prolonged exposure to a more concentrated solution of trifluoroacetic acid.

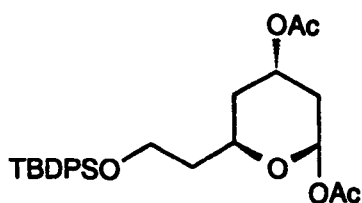
Trifluoroacetic acid (0.20ml, 2.6mmol) was added dropwise to a solution of the alcohol (**255**) (135mg, 0.26mmol) in THF (5ml) and water (1ml) at room temperature. The solution was stirred for 8h before addition of a saturated solution of sodium bicarbonate (10ml) and removal of the solvent *in vacuo*. The residue was extracted with ethyl acetate (4 x 20ml), the combined extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to leave a colourless oil. The oil was purified by chromatography on silica, eluting with 30% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *diol* (64mg, 61%) as a colourless oil.

(2*R*, 4*S*, 6*S*)-6-[2'-(*tert*-Butyl-diphenyl-silanyloxy)-ethyl]-tetrahydro-pyran-2,4-diol (257)



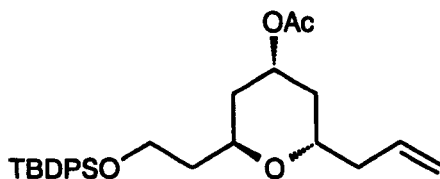
Ozone was bubbled through a solution of the diol (**256**) (80mg, 0.20mmol) in dichloromethane (10ml) at -78°C for 30min until the solution turned blue. Oxygen was then bubbled through for 10min until the solution went colourless. Triphenylphosphine (58mg, 0.22mmol) was then added in one portion and the solution was allowed to warm to room temperature over 1h. The solution was then stirred at room temperature for 12h and concentrated *in vacuo* to leave a solid residue. The residue was purified by chromatography on silica, eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), to give a 3:1 ratio of *hemi-acetal* anomers (57mg, 95%) as a colourless oil; ν_{\max} (soln., CHCl₃) 3597, 3532cm⁻¹; δ_{H} (360MHz) 7.72-7.66 (m, 4H, Ar), 7.47-7.37 (m, 6H, Ar), 5.24 (t, *J* 4.4, 1H, *H*-2), 4.49-4.41 (m, 1H, *H*-4), 4.17-4.10 (m, 1H, *H*-6), 3.90-3.77 (m, 2H, CH₂OTBDPS), 3.72 (d, *J* 5.8, 1H, OH), 3.08 (d, *J* 6.9, 1H, OH), 1.97-1.90 (m, 1H), 1.87-1.70 (m, 4H), 1.60-1.49 (m, 1H), 1.07 (s, 9H, SiC(CH₃)₃); δ_{C} (90MHz) 135.6 (d), 133.9 (s), 129.6 (d), 127.6 (d), 92.7 (d), 64.8 (d), 60.3 (t), 59.7 (d), 38.6 (t), 38.3 (t), 35.1 (t), 26.8 (q), 19.2 (s); *m/z* (FAB) Found: 423.1927, ([M+Na]⁺ C₂₃H₃₂O₄SiNa requires 423.1968).

(2*S*, 4*S*, 6*S*)-Acetic acid 2-acetoxy-6-[2'-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-tetrahydro-pyran-4-yl ester (258)



Triethylamine (0.10ml, 0.71mmol) and 4-dimethylaminopyridine (3mg, 29 μ mol) were added successively to a solution of the *hemi*-acetal (**257**) (57mg, 0.14mmol) in dichloromethane (5ml) at 0°C, under a nitrogen atmosphere. The solution was stirred for 5min before dropwise addition of acetic anhydride (54 μ l, 0.57mmol). The solution was allowed to warm up to room temperature and stirred for 1h before addition of 1M hydrochloric acid (0.2ml) and a saturated solution of sodium chloride (15ml). The organic residue was extracted with ethyl acetate (4 x 15ml), the combined extracts were then dried (Na₂SO₄) and concentrated *in vacuo* to leave a colourless oil. The oil was purified by chromatography on silica, eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give a 3:1 ratio of *bis*-acetate anomers (59mg, 86%) as a colourless oil; ν_{max} (soln., CDCl₃) 1730cm⁻¹; δ_{H} (360MHz) 7.70-7.65 (m, 4H, Ar), 7.46-7.37 (m, 6H, Ar), 6.19 (d, *J* 3.9, 1H, *H*-2), 5.14 (app. t, *J* 3.1, 1H, *H*-4), 4.60-4.53 (m, 1H, *H*-6), 3.89-3.69 (m, 2H, CH₂OTBDPS), 2.10 (s, 3H, OCOCH₃), 2.04 (s, 3H, OCOCH₃), 2.01-1.50 (m, 6H, 3x CH₂), 1.07 (s, 9H, SiC(CH₃)₃); δ_{C} (90MHz) 170.4 (s), 169.6 (s), 135.5 (d), 133.8 (s), 129.6 (d), 127.6 (d), 91.3 (d), 65.7 (d), 62.6 (d), 59.5 (t), 38.1 (t), 34.4 (t), 31.5 (t), 26.7 (q), 21.2 (2x q), 19.2 (s); *m/z* (FAB) Found: 507.2191, ([M+Na]⁺ C₂₇H₃₆O₆SiNa requires 507.2179).

(2*S*, 4*S*, 6*S*)-Acetic acid 2-allyl-6-[2'-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-tetrahydro-pyran-4-yl ester (260**)**

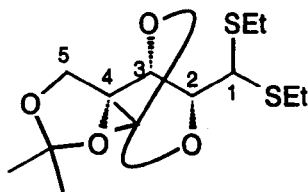


Allyltrimethylsilane (20 μ l, 0.13mmol) was added to a solution of the *bis*-acetate (**258**) (31mg, 64 μ mmol) in dichloromethane (1ml) and acetonitrile (1ml) at -78°C, under a nitrogen atmosphere. Boron trifluoride diethyl etherate (16 μ l, 0.13mmol) and trimethylsilyl trifluoromethanesulfonate (2.5 μ l, 13 μ mol) were then added successively

and the solution stirred at -78°C for 30min. A saturated solution of sodium bicarbonate (1ml) and then added and the mixture allowed to warm to room temperature. The biphasic mixture was extracted with ethyl acetate (3 x 15ml), the combined extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to leave a colourless oil. The oil was purified by chromatography on silica, eluting with 10% ethyl acetate in petroleum ether (b.p. $40\text{-}60^{\circ}\text{C}$), to give the *trans-tetrahydropyran* (28mg, 94%) as a colourless oil; $[\alpha]_{\text{D}} = -38.5$ ($c = 1.3$, CHCl_3); ν_{max} (soln., CHCl_3) 2931, 2859, 1725, 1367, 1111cm^{-1} ; δ_{H} (360MHz) 7.70-7.66 (m, 4H, Ar), 7.46-7.37 (m, 6H, Ar), 5.78-5.66 (m, 1H, $\text{CH}=\text{CH}_2$), 5.09-4.98 (m, 3H, $\text{CH}=\text{CH}_2$, $H-4$), 4.31 (dddd, J 9.4, 4.6, 4.6, 4.6, 1H, $H-6$), 3.81-3.67 (m, 2H, CH_2OTBDPS), 3.57 (dddd, J 9.6, 6.3, 6.3, 2.8, 1H, $H-2$), 2.36-2.28 (m, 1H, $\text{CHHCH}=\text{CH}_2$), 2.23-2.14 (m, 1H, $\text{CHHCH}=\text{CH}_2$), 2.05 (s, 3H, OCOCH_3), 2.04-1.94 (m, 2H, $H-5$, $H-1'$), 1.80-1.76 (m, 2H, $H-5$, $H-1'$), 1.75-1.64 (m, 1H, $H-3$), 1.34 (ddd, J 12.6, 9.9, 9.9, 1H, $H-3$), 1.06 (s, 9H, $\text{SiC}(\text{CH}_3)_3$); δ_{C} (90MHz) 170.4 (s), 135.6 (d), 134.5 (d), 133.8 (s), 129.6 (d), 127.6 (d), 117.0 (t), 68.4 (d), 68.3 (d), 67.7 (d), 60.6 (t), 40.0 (t), 36.2 (t), 34.5 (t), 34.4 (t), 26.8 (q), 21.3 (q), 19.2 (s); m/z (FAB) Found: 467.2610, ($[\text{MH}]^+$ $\text{C}_{28}\text{H}_{39}\text{O}_4\text{Si}$ requires 467.2618); Found: C, 72.2; H, 8.7%, $\text{C}_{28}\text{H}_{38}\text{O}_4\text{Si}$ requires C, 72.1; H, 8.2%.

3.3 Synthetic Studies Towards the Side Chain

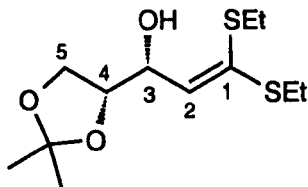
2,3:4,5-Di-*O*-isopropylidene-*D*-xylose diethyl dithioacetal (266)¹⁴⁹



Ethanethiol (50.0ml, 0.676mol) was added dropwise over 10min to a stirred solution of (*D*)-xylose (50.0g, 0.333mol) in 6M hydrochloric acid (400ml) at room temperature. The mixture was stirred for 2h and then neutralised with calcium carbonate (120g) until pH 7 was attained. The precipitated inorganic residue was removed by filtration and washed with toluene (500ml). The biphasic filtrate was concentrated *in vacuo* to leave the crude dithioacetal as an orange residue. The residue was taken up in acetone (1L), cooled to 0°C and then concentrated sulfuric acid (15ml) was added. The resulting solution was stirred for 16h and then neutralised by the addition of calcium hydroxide (50g). The precipitated solid was removed by filtration and washed with acetone (500ml). The filtrate was then concentrated *in vacuo* to leave a brown oil which was taken up in diethyl ether and washed with a saturated solution of sodium bicarbonate (600ml), a saturated solution of brine (600ml). The organic layer was then dried and the solvent removed *in vacuo* to leave the crude *bis*-acetonide (~70g) as a yellow oil. An analytical sample was purified by chromatography on silica, eluting with 10% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *bis*-acetonide as a pale yellow oil; $[\alpha]_D = -70.1$ ($c = 2.6$, acetone), [lit. -67.0 ($c = 2.8$, acetone)]¹⁴⁴; ν_{\max} (soln., CHCl_3) 2982, 2931, 1381, 1372, 1070 cm^{-1} ; δ_{H} (360MHz) 4.34 (m, 2H, *H*-2, *H*-3), 4.12 (dd, J 7.4, 3.1, 1H, *H*-4), 4.04 (dd, J 8.1, 6.7, 1H, *H*-5), 3.92 (t, J 7.6, 1H, *H*-5), 3.89 (d, J 5.2, 1H, *H*-1), 2.79-2.68 (m, 4H, $\text{S}(\text{CH}_2\text{CH}_3)_2$), 1.45 (s, 3H, CCH_3), 1.41 (s, 6H, 2x CCH_3), 1.36 (s, 3H, CCH_3), 1.26 (t, J 7.4, 3H, SCH_2CH_3), 1.25 (t, J 7.4, 3H, SCH_2CH_3); δ_{C} (90MHz) 110.0 (s), 109.4 (s), 80.0 (d), 78.6 (d), 75.2 (d), 65.8

(t), 53.0 (d), 27.3 (q), 27.1 (q), 26.1 (q), 25.5 (q), 25.3 (t), 24.9 (t), 14.3 (q), 14.2 (q); m/z (EI) Found: 336.1445, (M^+ $C_{15}H_{28}O_4S_2$ requires 336.1429).

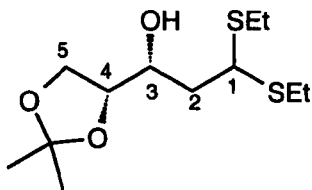
2-Deoxy-4,5-*O*-isopropylidene-*D*-threo-pent-1-enose diethyl dithioacetal (267)¹²³



A solution of the *bis*-acetonide (266) (~70g, 0.21mol) in THF (300ml) was added dropwise over 1h to a solution of potassium *t*-butoxide (30.4g, 0.271mol) in THF (750ml) and dimethylsulfoxide (300ml) at room temperature, under a nitrogen atmosphere. The solution was stirred for 1h and then poured onto ice (500g). The mixture was extracted with dichloromethane (3 x 400ml) and the combined organic extracts were washed with water (500ml) and dried (Na_2SO_4). The solution was concentrated *in vacuo* to leave a brown oil, which was purified by chromatography on silica, eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the allylic alcohol (32.8g, 35%, 3 steps) as a yellow oil; $[\alpha]_D = -54.4$ ($c = 2.4$, $CHCl_3$), [lit. -48.5 ($c = 2.4$, $CHCl_3$)]¹²³; ν_{max} (soln., $CHCl_3$) 3566 (br), 1374, 1065 cm^{-1} ; δ_H (360MHz) 5.85 (d, J 8.6, 1H, $H-2$), 4.75-4.70 (m, 1H, $H-3$), 4.03 (app. q, J 6.4, 1H, $H-4$), 3.91 (dd, J 8.4, 6.4, 1H, $H-5$), 3.73 (dd, J 8.4, 6.4, 1H, $H-5$), 2.86-2.66 (m, 5H, $S(CH_2CH_3)_2$, OH), 1.42 (s, 3H, CCH_3), 1.32 (s, 3H, CCH_3), 1.21 (t, J 7.4, 3H, SCH_2CH_3), 1.20 (t, J 7.4, 3H, SCH_2CH_3); δ_C (90MHz) 135.8 (s), 132.6 (d), 109.6 (s), 78.7 (d), 70.5 (d), 65.6 (t), 27.4 (t), 26.8 (t), 26.5 (q), 25.2 (q), 14.9 (q), 13.7 (q); m/z (EI) Found: 260.0908, ($[M-H_2O]^+$ $C_{12}H_{20}O_2S_2$ requires 260.0905); Found: C, 52.0; H, 8.1%, calc. for $C_{12}H_{22}O_3S_2$: C, 51.8; H, 8.0%.

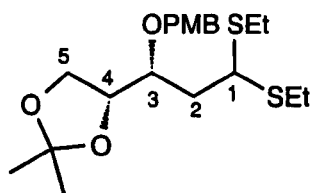
2-Deoxy-4,5-*O*-isopropylidene-*D*-threo-pentose diethyl dithioacetal

(268)¹²³



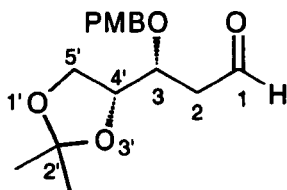
A solution of the allylic alcohol (267) (32.0g, 0.115mol) in THF (300ml) was added dropwise over 2h to a suspension of lithium aluminium hydride (10.0g, 0.264mol) in THF (800ml) at room temperature, under a nitrogen atmosphere. After the addition was complete the mixture was stirred for 3h. Residual lithium aluminium hydride was quenched by sequential addition of water (10ml), 2M sodium hydroxide (10ml) and water (20ml) over a 1h period. The resulting mixture was filtered through Celite, and the residual solid washed with diethyl ether (500ml). The filtrate was washed with brine (500ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the alcohol (29.1g, 90%) as a colourless oil; $[\alpha]_D = +26.3$ ($c = 3.9$, CHCl_3), [lit. $+25.6$ ($c = 5.0$, CHCl_3)]¹²³; ν_{max} (soln., CHCl_3) 3471(br), 1372, 1067 cm^{-1} ; δ_{H} (360MHz) 4.05 (dd, J 10.4, 4.2, 1H, *H*-1), 4.01-3.95 (m, 2H, *H*-4, *H*-5), 3.87 (ddd, J 10.0, 4.5, 2.5, 1H, *H*-3), 3.73 (dd, J 10.9, 9.5, 1H, *H*-5), 3.07 (br s, 1H, OH), 2.72-2.51 (m, 4H, $\text{S}(\text{CH}_2\text{CH}_3)_2$), 1.98 (ddd, J 14.2, 7.8, 4.2, 1H, *H*-2), 1.67 (ddd, J 14.2, 10.4, 2.5, 1H, *H*-2), 1.40 (s, 3H, CCH_3), 1.33 (s, 3H, CCH_3), 1.23 (t, J 7.4, 6H, $\text{S}(\text{CH}_2\text{CH}_3)_2$); δ_{C} (90MHz) 109.4 (s), 78.5 (d), 69.5 (d), 65.8 (t), 47.5 (d), 40.1 (t), 26.4 (q), 25.1 (q), 24.2 (t), 23.9 (q), 14.4 (q), 14.3 (q); m/z (EI) Found: 280.1160, ($\text{M}^+ \text{C}_{12}\text{H}_{24}\text{O}_3\text{S}_2$ requires 280.1167); Found: C, 51.4; H, 8.9; S, 23.0%, calc. for $\text{C}_{12}\text{H}_{24}\text{O}_3\text{S}_2$: C, 51.4; H, 8.6; S, 22.8%.

3-*O*-(4'-Methoxy-benzyl)-2-deoxy-4,5-*O*-isopropylidene-*D*-threo-pentose diethyl dithioacetal (269)



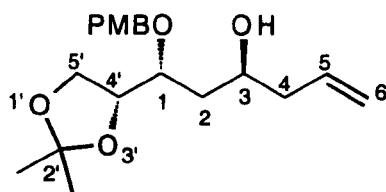
Potassium *t*-butoxide (2.21g, 19.7mmol) was added in one portion to a stirred solution of the alcohol (268) (4.60g, 16.4mmol) in THF (100ml) at -20°C , under a nitrogen atmosphere. The solution was stirred at -20°C for 1h, then tetrabutylammonium iodide (0.61g, 1.6mmol) and a solution of 4-methoxybenzyl bromide (4.62g, 23.0mmol) in THF (20ml) were added. The suspension was allowed to warm to room temperature and stirring was continued for 15h. Saturated ammonium chloride solution (50ml) was added and the solvent was removed *in vacuo*. The residue was extracted with ethyl acetate (3 x 75ml), the combined extracts were then dried and concentrated *in vacuo* to leave a yellow oil. The oil was purified by chromatography on silica, eluting with 10% ethyl acetate in petroleum ether (b.p. $40-60^{\circ}\text{C}$), to give the *4-methoxybenzyl ether* (6.41g, 98%) as a colourless oil; $[\alpha]_{\text{D}} = +34.0$ ($c = 2.4$, CHCl_3); ν_{max} (film) 1612, 854, 822cm^{-1} ; δ_{H} (360MHz) 7.29 (d, J 8.8, 2H, Ar), 6.89 (d, J 8.8, 2H, Ar), 4.75 (d, J 11.2, 1H, OCHHAr), 4.69 (d, J 11.2, 1H, OCHHAr), 4.25 (dd, J 13.2, 6.6, 1H, *H*-4), 4.00 (dd, J 8.3, 6.6, 1H, *H*-5), 3.94 (dd, J 10.6, 4.1, 1H, *H*-1), 3.94-3.88 (m, 1H, *H*-3), 3.82 (s, 3H, ArOCH_3), 3.74 (dd, J 8.3, 7.1, 1H, *H*-5), 2.71-2.52 (m, 4H, $\text{S}(\text{CH}_2\text{CH}_3)_2$), 2.00 (ddd, J 14.2, 9.6, 4.1, 1H, *H*-2), 1.75 (ddd, J 14.2, 10.6, 1.9, 1H, *H*-2), 1.47 (s, 3H, CCH_3), 1.38 (s, 3H, CCH_3), 1.24 (t, J 7.4, 6H, $\text{S}(\text{CH}_2\text{CH}_3)_2$); δ_{C} (90MHz) 159.2 (s), 130.7 (s), 129.5 (d), 113.7 (d), 109.4 (s), 77.7 (d), 76.9 (d), 72.9 (t), 65.6 (t), 55.2 (q), 47.5 (d), 37.3 (t), 26.4 (q), 25.1 (q), 24.3 (t), 23.4 (t), 14.4 (q), 14.3 (q); m/z (EI) Found: 400.1751, (M^+ $\text{C}_{20}\text{H}_{32}\text{O}_4\text{S}_2$ requires 400.1742).

(3*R*, 4'*R*)-3-(2',2'-Dimethyl-[1',3']-dioxolan-4'-yl)-3-(4''-methoxybenzyloxy)-propionaldehyde (270)



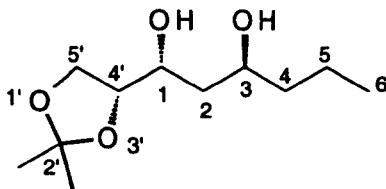
Calcium carbonate (0.28g, 2.85mmol) and a solution of mercury (II) perchlorate hydrate (0.76g, 1.90mmol) in water (4ml) were added successively in one portion to a solution of the dithioacetal (**269**) (0.38g, 0.95mmol) in THF (25ml). The resulting solution was stirred for 3h at room temperature, diethyl ether (50ml) was added and the suspension stirred for 15min. The suspension was filtered through a short pad of silica and the resulting solution was then dried (Na_2SO_4). The solvent removed *in vacuo* to leave a colourless oil, which was purified by chromatography on silica eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *aldehyde* (0.25g, 91%) as a colourless oil; $[\alpha]_{\text{D}} = +28.5$ ($c = 3.7$, CHCl_3); ν_{max} (film) 2729, 1725 cm^{-1} ; δ_{H} (360MHz) 9.73 (t, J 1.7, 1H, $H-1$), 7.24 (d, J 8.7, 2H, Ar), 6.88 (d, J 8.7, 2H, Ar), 4.59 (app. q, J 11.3, 2H, CH_2Ar), 4.32-4.27 (m, 1H, $H-5'$), 4.14-4.09 (m, 1H, $H-3$), 4.00 (dd, J 8.6, 6.8, 1H, $H-4'$), 3.83-3.79 (m, 1H, $H-5'$), 3.80 (s, 3H, ArOCH_3), 2.61 (ddd, J 7.0, 1.7, 1.7, 2H, $H-2$), 1.44 (s, 3H, CCH_3), 1.36 (s, 3H, CCH_3); δ_{C} (90MHz) 200.7 (d), 159.3 (s), 129.9 (s), 129.6 (d), 113.8 (d), 109.7 (s), 76.3 (d), 73.6 (d), 72.4 (t), 65.2 (t), 55.2 (q), 44.4 (t), 26.2 (q), 24.9 (q); m/z (EI) Found: 294.1460, ($\text{M}^+ \text{C}_{16}\text{H}_{22}\text{O}_5$ requires 294.1467).

(1*R*, 3*S*, 4'*R*)-1-(2',2'-Dimethyl-[1',3']-dioxolan-4'-yl)-1-(4''-methoxy-benzyloxy)-hex-5-en-3-ol (271)



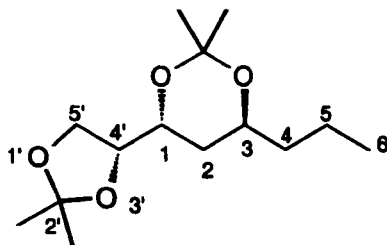
(-)- β -Methoxydiisopinocampheylborane (7.00g, 22.2mmol) was dissolved in anhydrous diethyl ether (250ml) and cooled to -78°C , under an argon atmosphere. Allylmagnesium bromide (20.5ml, 1.0M in Et_2O , 20.5mmol) was added dropwise over 15min, at -78°C and then warmed to room temperature and stirred for 1h. The suspension was then recooled to -78°C and a solution of the aldehyde (270) (5.10g, 17.1mmol) in diethyl ether (60ml) was added dropwise over 15min. The suspension was stirred at -78°C for 3h and then quenched with methanol (4ml). A solution of 2M sodium hydroxide (100ml) and hydrogen peroxide (100ml) were added and the biphasic mixture refluxed for 2h. The mixture was then cooled and the organic layer was separated. The aqueous layer was then extracted with ethyl acetate (3 x 100ml), dried (Na_2SO_4) and the combined organic extracts were concentrated *in vacuo* to leave a colourless oil. The oil was then purified by chromatography on silica, eluting with 20% ethyl acetate in petroleum ether (b.p. $40\text{--}60^{\circ}\text{C}$), to give the *alcohol* (4.69g, 82%) as a colourless oil; ν_{max} (film) 3474 (br), 1612cm^{-1} ; δ_{H} (360MHz) 7.30 (d, J 8.6, 2H, Ar), 6.90 (d, J 8.6, 2H, Ar), 5.85–5.73 (m, 1H, H -5), 5.13–5.08 (m, 2H, H -6), 4.76 (d, J 11.3, 1H, OCHHAr), 4.61 (d, J 11.3, 1H, OCHHAr), 4.26 (ddd, J 7.2, 6.6, 6.6, 1H, H -4'), 4.07–3.97 (m, 2H, H -5'), 3.93–3.86 (m, 1H, H -3), 3.82 (s, 3H, ArOCH_3), 3.67 (dd, J 8.1, 7.6, 1H, H -1), 2.23–2.19 (m, 2H, H -4), 1.65–1.45 (m, 2H, H -2) 1.46 (s, 3H, CCH_3), 1.40 (s, 3H, CCH_3); δ_{C} (90MHz) 159.3 (s), 134.4 (d), 130.3 (s), 129.8 (d), 118.0 (t), 113.9 (d), 109.6 (s), 78.4 (d), 76.5 (d), 72.8 (t), 68.0 (d), 65.9 (t), 55.3 (q), 42.0 (t), 37.0 (t), 26.5 (q), 25.4 (q); m/z (EI) Found: 336.1931, ($\text{M}^+ \text{C}_{19}\text{H}_{28}\text{O}_5$ requires 336.1937).

(1*R*, 3*S*, 4'*R*)-1-(2',2'-Dimethyl-[1',3']-dioxolan-4'-yl)-hexan-1,3-diol
(273)



Palladium on carbon (30mg, 10%) was added in one portion to a solution of the alcohol (271) (90mg, 0.27mmol) in methanol (5ml). The flask was purged with hydrogen and stirred under a hydrogen atmosphere for 24h. The suspension was filtered through Celite and the solid residue was then washed with dichloromethane (50ml). The filtrate was concentrated *in vacuo* to leave a yellow oil which was purified by chromatography on silica, eluting with 40% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *diol* (47mg, 81%) as a colourless oil; $[\alpha]_D = +18.9$ ($c = 1.6$, CHCl_3); ν_{max} (film) 3426 (br) cm^{-1} ; δ_{H} (360MHz) 4.06-3.91 (m, 3H, *H*-1, *H*-4', *H*-5'), 3.87-3.83 (m, 1H, *H*-3), 3.76-3.70 (m, 1H, *H*-5'), 1.67-1.59 (m, 1H), 1.54-1.30 (m, 5H), 1.43 (s, 3H, CCH_3), 1.37 (s, 3H, CCH_3), 0.92 (t, J 7.0, 3H, *H*-6); δ_{C} (90MHz) 109.5 (s), 79.1 (d), 69.5 (d), 68.4 (d), 66.0 (t), 39.6 (2x t), 26.6 (q), 25.2 (q), 18.8 (t), 14.0 (q); m/z (EI) Found: 203.1278, ($[\text{M-Me}]^+ \text{C}_{10}\text{H}_{19}\text{O}_4$ requires 203.1283).

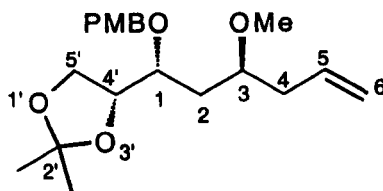
(1*R*, 3*S*, 4'*R*)-1-(2',2'-Dimethyl-[1',3']-dioxolan-4'-yl)-1,3-*O*-isopropylidene-hexan-1,3-diol (274)



p-Toluenesulfonic acid monohydrate (4mg, 20 μ mol) was added to a solution of the diol (273) (25mg, 0.11mmol) in 2,2-dimethoxypropane (5ml) at 0°C, under a nitrogen

atmosphere. The solution was stirred for 10min and the solvent was then removed *in vacuo*. The residue was purified by chromatography on silica, eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *bis-acetonide* (30mg, 100%) as a colourless oil; $[\alpha]_D = +42.5$ ($c = 0.6$, CHCl_3); ν_{max} (film) 2985, 1456, 1378, 1224, 1071 cm^{-1} ; δ_{H} (360MHz) 4.13 (dd, J 13.3, 6.6, 1H, $H-5'$), 4.03 (dd, J 8.3, 6.6, 1H, $H-5'$), 3.86 (ddd, J 9.6, 6.6, 6.6, 1H, $H-1$), 3.81-3.77 (m, 1H, $H-3$), 3.72 (dd, J 8.3, 6.9, 1H, $H-4'$), 1.67-1.61 (m, 1H), 1.55-1.28 (m, 5H), 1.43 (s, 3H, CCH_3), 1.38 (s, 3H, CCH_3), 1.37 (s, 3H, CCH_3), 1.37 (s, 3H, CCH_3), 0.92 (t, J 7.0, 3H, $H-6$); δ_{C} (90MHz) 109.8 (s), 100.6 (s), 77.8 (d), 67.9 (d), 66.2 (d), 65.4 (t), 37.9 (t), 34.0 (t), 26.5 (q), 25.3 (q), 24.5 (2x q), 18.5 (t), 13.9 (q); m/z (EI) Found: 243.1599, ($[\text{M-Me}]^+ \text{C}_{13}\text{H}_{23}\text{O}_4$ requires 243.1596).

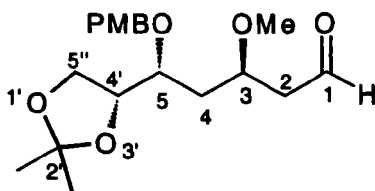
(1*R*, 3*S*, 4'*R*)-1-(2',2'-Dimethyl-[1',3']-dioxolan-4'-yl)-3-methoxy-1-(4''-methoxy-benzyloxy)-hex-5-ene (272)



Potassium *t*-butoxide (2.27g, 20.2mmol) was added in one portion to a stirred solution of the alcohol (271) (3.40g, 10.1mmol) in THF (100ml) at -20°C, under a nitrogen atmosphere. The solution was stirred at -20°C for 30min and then methyl iodide (6.30ml, 101mmol) was added dropwise over 10min. The solution was allowed to warm up to room temperature and then stirred for 6h. Saturated ammonium chloride solution (50ml) was added and the solvent was removed *in vacuo*. The residue was extracted with ethyl acetate (4 x 100ml), the combined extracts were then dried and concentrated *in vacuo* to leave a yellow oil which was purified by chromatography on silica, eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *methyl ether* (3.43g, 97%) as a colourless oil; $[\alpha]_D = +63.7$ ($c = 2.3$, CHCl_3); ν_{max}

(soln., CHCl_3) 1612cm^{-1} ; δ_{H} (360MHz) 7.30 (d, J 8.6, 2H, Ar), 6.88 (d, J 8.6, 2H, Ar), 5.82-5.70 (m, 1H, H -5), 5.11-5.05 (m, 2H, H -6), 4.76 (d, J 11.1, 1H, OCHHAr), 4.55 (d, J 11.1, 1H, OCHHAr), 4.19 (dd, J 13.9, 6.7, 1H, H -5'), 3.98 (dd, J 8.2, 6.7, 1H, H -4'), 3.81 (s, 3H, ArOCH_3), 3.73-3.66 (m, 2H, H -5', H -1), 3.48-3.42 (m, 1H, H -3), 3.26 (s, 3H, OCH_3), 2.30-2.26 (m, 2H, H -4), 1.58-1.50 (m, 1H, H -2), 1.46 (s, 3H, CCH_3), 1.44-1.34 (m, 1H, H -2), 1.38 (s, 3H, CCH_3); δ_{C} (90MHz) 159.1 (s), 134.1 (d), 130.9 (s), 129.6 (d), 117.3 (t), 113.7 (d), 109.2 (s), 78.8 (d), 76.2 (d), 76.1 (d), 72.8 (t), 65.9 (t), 56.3 (q), 55.1 (q), 37.5 (t), 36.1 (t), 26.5 (q), 25.3 (q); m/z (EI) Found: 350.2102, (M^+ $\text{C}_{20}\text{H}_{30}\text{O}_5$ requires 350.2093); Found: C, 68.7; H, 8.8%, $\text{C}_{20}\text{H}_{30}\text{O}_5$ requires C, 68.6; H, 8.6%.

(3*S*, 5*R*, 4'*R*)-5-(2',2'-Dimethyl-[1',3']-dioxolan-4'-yl)-3-methoxy-5-(4''-methoxy benzyloxy)-pentanal (275)

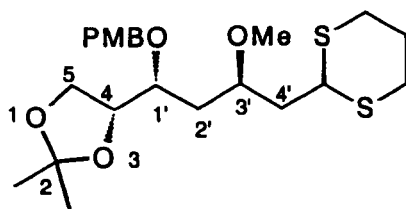


4-Methylmorpholine *N*-oxide (0.23g, 1.7mmol), followed by osmium tetroxide (20mg, cat.) were added to a solution of the methyl ether (272) (0.20g, 0.57mmol) in acetone (20ml) and water (2ml). The solution was stirred at room temperature for 12h and then a saturated solution of sodium thiosulfate (20ml) was added. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (50ml) and the organic layer separated. The aqueous phase was extracted with ethyl acetate (3 x 50ml) and the combined organic layers were dried (Na_2SO_4) and the solvent removed *in vacuo* to leave a colourless oil, which was used immediately without purification.

An aqueous solution of sodium periodate (0.18g, 0.82mmol, 0.65M) was added dropwise over 5min to a vigorously stirred suspension of silica (1.5g) in dichloromethane (20ml). The crude diol in dichloromethane (5ml) was then added

dropwise over 2min and the suspension stirred for 1h. The suspension was filtered and the silica was washed with dichloromethane (200ml). The solvent was removed *in vacuo* to leave a colourless oil which was purified by chromatography on silica, eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *aldehyde* (0.19g, 96%) as a colourless oil; $[\alpha]_D = +60.7$ ($c = 1.8$, CHCl_3); ν_{max} (film) 2727, 1723 cm^{-1} ; δ_{H} (360MHz) 9.78 (t, J 2.2, 1H, $H-1$), 7.30 (d, J 8.6, 2H, Ar), 6.89 (d, J 8.6, 2H, Ar), 4.76 (d, J 11.2, 1H, OCHHAr), 4.54 (d, J 11.2, 1H, OCHHAr), 4.22 (ddd, J 6.7, 6.7, 6.6, 1H, $H-4'$), 3.99 (dd, J 8.2, 6.7, 1H, $H-5'$), 3.91-3.82 (m, 1H, $H-5$), 3.81 (s, 3H, ArOCH_3), 3.78-3.65 (m, 2H, $H-5'$, $H-3$), 3.25 (s, 3H, OCH_3), 2.61 (dd, J 5.6, 2.2, 2H, $H-2$), 1.64-1.53 (m, 2H, $H-4$), 1.46 (s, 3H, CCH_3), 1.38 (s, 3H, CCH_3); δ_{C} (90MHz) 201.0 (s), 159.2 (s), 130.5 (s), 129.7 (d), 113.8 (d), 109.4 (s), 78.1 (d), 75.8 (d), 72.8 (d), 72.7 (t), 65.7 (t), 56.7 (q), 55.2 (q), 48.0 (t), 36.4 (t), 26.4 (q), 25.2 (q); m/z (EI) Found: 351.1854, $([\text{M}-\text{H}]^+ \text{C}_{19}\text{H}_{27}\text{O}_6)$ requires 351.1867).

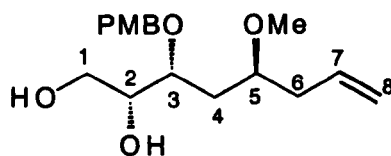
(4*R*, 1'*R*, 3'*S*)-4-[4'-[1'',3'']-Dithian-2''-yl-3'-methoxy-1'-(4'''-methoxy-benzyloxy)-butyl]-2,2-dimethyl-[1,3]-dioxolane (276)



Zinc iodide (7mg, 23 μmol) was added to a solution of the aldehyde (**275**) (80mg, 0.23mmol) in diethyl ether (3ml) at room temperature, under a nitrogen atmosphere. 1,3-*bis*-(Trimethylsilylthio)propane (64mg, 0.25mmol) was added dropwise over 1min and the cloudy suspension was stirred at room temperature for 1h. The reaction was quenched with water (5ml), and extracted with ethyl acetate (3 x 15ml), the combined extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to leave a colourless oil. The oil was purified by chromatography on silica eluting with 20% ethyl acetate in

petroleum ether (b.p. 40-60°C), to give the *dithiane* (15mg, 15%) as a colourless oil; ν_{\max} (soln., CHCl_3) 2984, 2935, 2836, 1612, 1372, 1074 cm^{-1} ; δ_{H} (360MHz) 7.31 (d, J 8.6, 2H, Ar), 6.88 (d, J 8.6, 2H, Ar), 4.74 (d, J 11.1, 1H, OCHHAr), 4.56 (d, J 11.1, 1H, OCHHAr), 4.23-4.18 (m, 1H, H -5), 4.11 (t, J 7.1, 1H, H -1'), 3.97 (dd, J 8.3, 6.6, 1H, H -4), 3.81 (s, 3H, ArOCH_3), 3.74-3.65 (m, 3H, H -3', H -5, CHS_2), 3.28 (s, 3H, OCH_3), 2.99-2.75 (m, 4H, 2x CH_2S), 2.15-1.76 (m, 4H), 1.64-1.50 (m, 2H), 1.46 (s, 3H, CCH_3), 1.38 (s, 3H, CCH_3); δ_{C} (90MHz) 159.2 (s), 130.8 (s), 129.7 (d), 113.8 (d), 109.4 (s), 78.3 (d), 76.1 (d), 74.1 (d), 72.7 (t), 65.8 (t), 56.6 (q), 55.3 (q), 43.5 (d), 40.0 (t), 36.3 (t), 30.4 (2x t), 26.6 (q), 25.9 (t), 25.3 (q); m/z (EI) Found: 427.1609, ($[\text{M}-\text{Me}]^+$ $\text{C}_{21}\text{H}_{31}\text{O}_5\text{S}_2$ requires 427.1613).

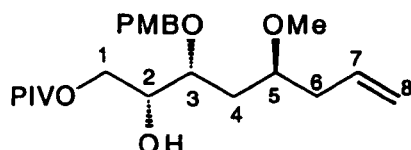
(2R, 3R, 5S)-5-Methoxy-3-(4'-methoxy-benzyloxy)-oct-7-ene-1,2-diol
(277)



10Camphorsulfonic acid (37mg, 0.16mmol) was added to a solution of the acetamide (272) (55mg, 0.16mmol) in methanol (5ml) at 0°C. The solution was stirred for 4h, whilst allowing to warm to room temperature. Saturated sodium bicarbonate solution (10ml) was added and the solvent removed *in vacuo*. The aqueous phase was then extracted with ethyl acetate (3 x 20ml), the combined extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to leave a yellow oil. The oil was purified by chromatography on silica eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *diol* (0.31g, 88%) as a colourless oil; $[\alpha]_{\text{D}} = +3.7$ ($c = 1.4$, CHCl_3); ν_{\max} (film) 3574 (br), 1613 cm^{-1} ; δ_{H} (360MHz) 7.29 (d, J 8.7, 2H, Ar), 6.91 (d, J 8.7, 2H, Ar), 5.84-5.74 (m, 1H, H -7), 5.14-5.10 (m, 2H, H -8), 4.55 (app. q, J 11.1, 2H, OCH_2Ar), 3.82 (s, 3H, ArOCH_3), 3.72-3.62 (m, 4H, H -1, H -2, H -3), 3.46-3.39 (m, 1H, H -5), 3.35 (s, 3H, OCH_3), 3.05 (d, J 3.9, 1H, CHOH), 2.77 (br s, 1H, CH_2OH), 2.36-2.29 (m, 2H, H -6), 1.75-1.71 (m, 2H, H -4); δ_{C} (90MHz) 159.3 (s),

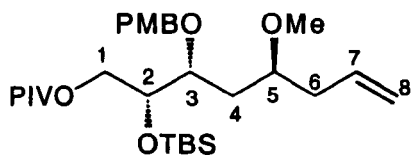
133.8 (d), 130.2 (s), 129.5 (d), 117.6 (t), 113.8 (d), 76.9 (d), 76.6 (d), 73.7 (d), 72.7 (t), 63.8 (t), 56.0 (q), 55.2 (q), 37.3 (t), 35.9 (t); m/z (EI) Found: 310.1780, (M^+ $C_{17}H_{26}O_5$ requires 310.1780).

(2*R*, 3*R*, 5*S*)-2',2'-Dimethyl-propionic acid 2-hydroxy-5-methoxy-3-(4''-methoxy-benzyloxy)-oct-7-enyl ester (278)



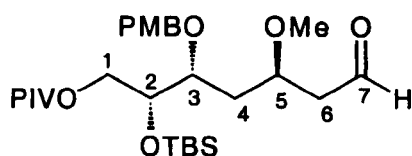
Trimethylacetyl chloride (8.7 μ l, 80 μ mol) and 4-dimethylaminopyridine (1mg) were added to a solution of the diol (**277**) (20mg, 60 μ mol) in pyridine (1ml) at 0°C, under a nitrogen atmosphere. The solution was allowed to warm to room temperature over 30min and stirred for a further 12h. Hydrochloric acid (10ml, 2M) and ethyl acetate (15ml) were added and the organic layer was separated. The aqueous fraction was extracted with ethyl acetate (2 x 15ml) and the combined organic layers were then dried (Na_2SO_4) and concentrated *in vacuo* to leave a yellow oil. The oil was purified by chromatography on silica eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *ester* (23mg, 92%) as a colourless oil; $[\alpha]_D = +10.3$ ($c = 2.9$, $CHCl_3$); ν_{max} (film) 3468 (br), 1728 cm^{-1} ; δ_H (360MHz) 7.27 (d, J 8.6, 2H, Ar), 6.99 (d, J 8.6, 2H, Ar), 5.84-5.73 (m, 1H, $H-7$), 5.12-5.04 (m, 2H, $H-8$), 4.53 (app. q, J 11.0, 2H, OCH_2Ar), 4.15 (d, J 5.8, 2H, $H-1$), 3.81 (s, 3H, $ArOCH_3$), 3.80 (obs. m, 1H, $H-2$), 3.72-3.68 (m, 1H, $H-3$), 3.45-3.37 (m, 1H, $H-5$), 3.33 (s, 3H, OCH_3), 2.51 (br s, 1H, $CHOH$), 2.34-2.27 (m, 2H, $H-6$), 1.80-1.67 (m, 2H, $H-4$), 1.22 (s, 9H, $COC(CH_3)_3$); δ_C (90MHz) 178.6 (s), 159.4 (s), 133.9 (d), 130.2 (s), 129.6 (d), 117.7 (t), 113.9 (d), 76.8 (d), 75.7 (d), 73.0 (t), 71.7 (d), 65.4 (t), 56.0 (q), 55.3 (q), 38.8 (s), 37.4 (t), 35.9 (t), 27.2 (q); m/z (EI) Found: 394.2358, (M^+ $C_{22}H_{34}O_6$ requires 394.2355).

(2R, 3R, 5S)-2',2'-Dimethyl-propionic acid 2-(*tert*-butyl-dimethyl-silanyloxy)-5-methoxy-3-(4''-methoxy-benzyloxy)-oct-7-enyl ester (279)



Triethylamine (0.20ml, 1.42mmol) was added in one portion to a solution of the alcohol (278) (0.28g, 0.71mmol) in dichloromethane (10ml) at 0°C, under a nitrogen atmosphere. The solution was stirred for 5min before *tert*-butyldimethylsilyl triflate (0.20ml, 0.85mmol) was added dropwise over 1min. The solution was stirred for a further 2h while allowing to warm to room temperature. A saturated solution of ammonium chloride (20ml) was added and the organic layer was separated. The aqueous phase was extracted with dichloromethane (3 x 25ml) and the combined organic layers were then dried and concentrated *in vacuo* to leave a yellow oil. The oil was purified by chromatography on silica eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *silyl ether* (0.36g, 100%) as a colourless oil; $[\alpha]_D = +43.4$ ($c = 2.5$, CHCl_3); ν_{max} (film), 1729, 1612 cm^{-1} ; δ_{H} (360MHz) 7.27 (d, J 8.7, 2H, Ar), 6.88 (d, J 8.7, 2H, Ar), 5.82-5.73 (m, 1H, H -7), 5.09-5.03 (m, 2H, H -8), 4.59 (d, J 11.4, 1H, OCHHAr), 4.49 (d, J 11.4, 1H, OCHHAr), 4.30 (ddd, J 10.5, 6.1, 6.1, 1H, H -2), 4.01-3.95 (m, 2H, H -1), 3.80 (s, 3H, ArOCH_3), 3.68 (ddd, J 10.5, 3.7, 1.9, 1H, H -3), 3.42-3.36 (m, 1H, H -5), 3.25 (s, 3H, OCH_3), 2.31-2.22 (m, 2H, H -6), 1.79-1.72 (m, 1H, H -4), 1.53-1.45 (m, 1H, H -4), 1.21 (s, 9H, $\text{COC}(\text{CH}_3)_3$), 0.89 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 0.07 (s, 3H, SiCH_3), 0.06 (s, 3H, SiCH_3); δ_{C} (90MHz) 178.5 (s), 159.2 (s), 134.5 (d), 130.8 (s), 129.4 (d), 117.1 (t), 113.8 (d), 76.7 (d), 76.6 (d), 72.4 (t), 70.6 (d), 65.7 (t), 56.0 (q), 55.2 (q), 38.7 (s), 37.9 (t), 34.3 (t), 27.3 (q), 25.7 (q), 18.0 (s), -4.7 (2x q); m/z (EI) Found: 451.2510, ($[\text{M}-t\text{Bu}]^+$ $\text{C}_{24}\text{H}_{39}\text{O}_6\text{Si}$ requires 451.2516).

(3*S*, 5*R*, 6*R*)-2',2'-Dimethyl-propionic acid 2-(*tert*-butyl-dimethyl-silanyloxy)-5-methoxy-3-(4''-methoxy-benzyloxy)-7-oxo-heptyl ester (280)

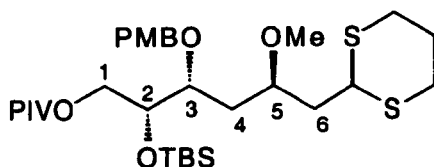


4-Methylmorpholine *N*-oxide (0.29g, 2.1mmol), followed by osmium tetroxide (20mg, cat.) were added to a solution of the silyl ether (**279**) (0.36g, 0.71mmol) in acetone (15ml) and water (1.5ml). The solution was stirred at room temperature for 12h and then a saturated solution of sodium thiosulfate (20ml) was added. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (50ml) and the organic phase separated. The aqueous phase was extracted with ethyl acetate (3 x 50ml) and the combined organic layers were dried (Na₂SO₄). The solvent was removed *in vacuo* to leave a colourless oil, which was used immediately without purification.

An aqueous solution of sodium periodate (0.22g, 1.0mmol, 0.65M) was added dropwise over 5min to a vigorously stirred suspension of silica (2g) in dichloromethane (20ml). The crude diol in dichloromethane (5ml) was then added dropwise over 2min and the suspension stirred for 1h. The suspension was filtered and the silica was washed with dichloromethane (200ml). The solvent was removed *in vacuo* to leave a colourless oil which was purified by chromatography on silica, eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *aldehyde* (0.34g, 93%) as a colourless oil; $[\alpha]_D = +45.0$ ($c = 3.0$, CHCl₃); ν_{\max} (film) 2723, 1727cm⁻¹; δ_H (360MHz) 9.74 (dd, J 2.2, 1.8, 1H, *H*-7), 7.24 (d, J 8.5, 2H, Ar), 6.85 (d, J 8.5, 2H, Ar), 4.57 (d, J 11.4, 1H, OCHHAr), 4.44 (d, J 11.4, 1H, OCHHAr), 4.30 (dd, J 11.2, 11.7, 1H, *H*-1), 4.02-3.98 (m, 1H, *H*-2), 3.92, (dd, J 11.2, 6.9, 1H, *H*-1), 3.81-3.76 (m, 1H, *H*-3), 3.76 (s, 3H, ArOCH₃), 3.62 (ddd, J 10.3, 4.1, 1.3, 1H, *H*-5), 3.22 (s, 3H, OCH₃), 2.56 (dd, J 3.8, 2.2, 2H, *H*-6), 1.96 (ddd, J 14.3, 8.9, 1.6, 1H, *H*-4), 1.46 (ddd, J 14.3, 10.6, 3.8, 1H, *H*-4), 1.18 (s, 9H, COC(CH₃)₃), 0.86

(s, 9H, SiC(CH₃)₃), 0.05 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃); δ_C (90MHz) 201.0 (d), 178.3 (s), 159.2 (s), 130.3 (s), 129.4 (d), 113.7 (d), 76.7 (d), 73.3 (d), 72.1 (t), 69.9 (d), 65.4 (t), 56.4 (q), 55.1 (q), 48.2 (t), 38.6 (s), 34.5 (t), 27.1 (q), 25.6 (q), 17.8 (s), -4.8 (2x q); m/z (EI) Found: 421.2031, ([M-*t*Bu-MeOH]⁺ C₂₂H₃₄O₆Si requires 421.2047).

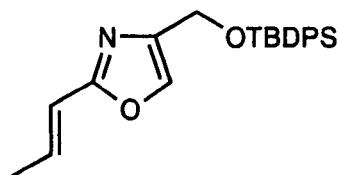
(3*S*, 5*R*, 6*R*)-2',2'-Dimethyl-propionic acid 2-(*tert*-butyl-dimethyl-silanyloxy)-6-[1'',3'']-dithian-2''-yl-5-methoxy-3-(4'''-methoxy-benzyloxy)-hexyl ester (281)



Zinc iodide (17mg, 0.055mmol) was added to a solution of the aldehyde (280) (0.28g, 0.23mmol) in diethyl ether (10ml) at room temperature, under a nitrogen atmosphere. 1,3-*bis*-(Trimethylsilylthio)propane (0.15g, 0.60mmol) was added dropwise and the cloudy suspension was then stirred at room temperature for 8h. The reaction was quenched with water (10ml), extracted with ethyl acetate (3 x 30ml) and the combined extracts were then dried (Na₂SO₄). The organic extracts were concentrated *in vacuo* to leave a colourless oil, which was purified by chromatography eluting with 10% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *dithiane* (0.20g, 73% based on recovered starting material); $[\alpha]_D = +21.0$ (c = 2.1, CHCl₃); ν_{\max} (soln., CHCl₃) 1721, 1612cm⁻¹; δ_H (360MHz) 7.29 (d, *J* 8.6, 2H, Ar), 6.87 (d, *J* 8.6, 2H, Ar), 4.57 (d, *J* 11.2, 1H, OCHHAr), 4.52 (d, *J* 11.2, 1H, OCHHAr), 4.31 (d, *J* 8.5, 1H, *H*-1), 4.12 (dd, *J* 7.9, 6.4, 1H, CHS₂), 4.01-3.93 (m, 2H, *H*-1, *H*-2), 3.80 (s, 3H, ArOCH₃), 3.66-3.59 (m, 2H, *H*-3, *H*-5), 3.27 (s, 3H, OCH₃), 2.93-2.78 (m, 4H, 2x CH₂S), 2.15-1.78 (m, 5H), 1.50 (ddd, *J* 14.1, 10.4, 3.6, 1H, *H*-4), 1.21 (s, 9H, COC(CH₃)₃), 0.88 (s, 9H, SiC(CH₃)₃), 0.07 (s, 3H, SiCH₃), 0.06 (s, 3H, SiCH₃); δ_C

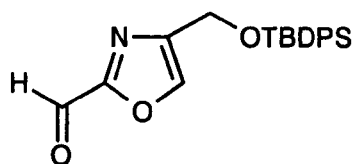
(90MHz) 178.4 (s), 159.1 (s), 130.5 (s), 129.4 (d), 113.7 (d), 77.0 (d), 74.5 (d), 72.1 (t), 70.2 (d), 65.5 (t), 56.1 (q), 55.1 (q), 43.5 (d), 40.2 (t), 38.6 (s), 34.2 (t), 30.3 (t), 30.1 (t), 27.2 (q), 25.8 (t), 25.6 (q), 17.8 (s), -4.7 (q), -4.8 (q); m/z (FAB) Found: 601.3024, $([MH]^+ C_{30}H_{53}O_6S_2Si$ requires 601.3053).

(E)-4-(*tert*-Butyl-diphenyl-silanyloxymethyl)-2-propenyl-oxazole (282)



Triethylamine (1.15ml, 8.3mmol) was added in one portion to a solution of the oxazole alcohol (**206**) (0.69g, 4.1mmol) in dichloromethane (20ml) at 0°C under a nitrogen atmosphere. The solution was stirred for 15min before addition of 4-dimethylaminopyridine (30mg, 0.25mmol) followed by dropwise addition of *tert*-butyldiphenylsilyl chloride (1.4ml, 5.4mmol). The solution was stirred for 16h whilst warming to room temperature. A saturated solution of ammonium chloride (20ml) was then added and the organic phase was separated and the aqueous layer extracted with dichloromethane (3 x 40ml). The organic extracts were combined, dried and concentrated *in vacuo* to leave a colourless oil. The oil was purified by chromatography on silica, eluting with 10% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *silyl ether* (1.56g, 100%) as a colourless oil; ν_{\max} (film) 3070, 3049, 2958, 2930, 2856, 1428, 1112, 702cm⁻¹; δ_H (360MHz) 7.76-7.73 (m, 4H, Ar), 7.48-7.35 (m, 7H, Ar, *H*-5), 6.71 (dq, *J* 15.9, 6.9, 1H, CH=CHCH₃), 6.28 (dq, *J* 15.9, 1.7, 1H, OX-CH=CH), 4.70 (d, *J* 1.3, 2H, CH₂OTBDPS), 1.92 (dd, *J* 6.9, 1.7, 3H, CH=CHCH₃), 1.11 (s, 9H, SiC(CH₃)₃); δ_C (125MHz) 161.2 (s), 141.5 (s), 134.8 (d), 134.1 (d), 133.1 (s), 129.7 (d), 127.7 (d), 127.5 (d), 117.8 (d), 59.4 (t), 26.7 (q), 19.2 (s), 18.3 (q); m/z (EI) Found: 320.1097 ($[M-tBu]^+ C_{19}H_{18}NO_2Si$ requires 320.1107).

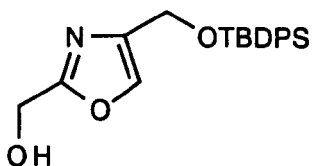
4-(*tert*-Butyl-diphenyl-silanyloxymethyl)-oxazole-2-carbaldehyde (283)



4-Methylmorpholine *N*-oxide (1.51g, 11.1mmol), followed by osmium tetroxide (20mg, cat.) were added to a solution of the oxazole (282) (1.4g, 3.7mmol) in acetone (30ml) and water (3ml). The solution was stirred at room temperature for 12h and then a saturated solution of sodium thiosulfate (40ml) was added. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (50ml) and the organic phase separated. The aqueous phase was extracted with ethyl acetate (3 x 50ml) and the combined organic layers were dried (Na₂SO₄). The solvent was removed *in vacuo* to leave a colourless oil, which was used immediately without purification.

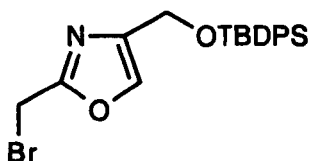
An aqueous solution of sodium periodate (0.82g, 3.8mmol, 0.65M) was added dropwise over 5min to a vigorously stirred suspension of silica (5g) in dichloromethane (50ml). The crude diol in dichloromethane (10ml) was then added dropwise over 2min and the suspension stirred for 2h. The suspension was filtered and the silica was washed with dichloromethane (200ml), the solvent was removed *in vacuo* to give the *aldehyde* (0.94g, 69%) as a colourless oil; ν_{\max} (film) 2857, 1708cm⁻¹; δ_{H} (360MHz) 9.73 (s, 1H, CHO), 7.77 (s, 1H, *H*-5), 7.75-7.71 (m, 4H, Ar), 7.48-7.40 (m, 6H, Ar), 5.29 (s, 2H, CH₂OTBDPS), 1.12 (s, 9H, SiC(CH₃)₃); δ_{C} (90MHz) 177.3 (d), 157.8 (s), 144.2 (s), 138.9 (d), 135.4 (d), 132.7 (s), 130.0 (d), 127.8 (d), 59.0 (t), 29.7 (q), 19.2 (s); *m/z* (EI) Found: 308.0745 ([M-*t*Bu]⁺ C₁₇H₁₄NO₃Si requires 308.0743).

[4-(*tert*-Butyl-diphenyl-silanyloxymethyl)-oxazol-2-yl] methanol (284)



Sodium borohydride (0.28g, 7.4mmol) was added in one portion to a solution of the aldehyde (283) (0.90g, 2.5mmol) in methanol (30ml) at 0°C, under a nitrogen atmosphere. The solution was stirred for 90min at 0°C and then a saturated solution of ammonium chloride (20ml) was added and the solvent removed *in vacuo*. A saturated solution of brine (100ml) was added and the mixture was extracted with ethyl acetate (3 x 50ml), the combined extracts were then dried (Na₂SO₄) and concentrated *in vacuo* to give the *alcohol* (0.9g, 100%) as a colourless oil, which was used without further purification; ν_{max} (film) 3296 (br), 1576, 1112cm⁻¹; δ_{H} (360MHz) 7.70-7.68 (m, 4H, Ar), 7.48 (t, *J* 1.3, 1H, *H*-5), 7.47-7.36 (m, 6H, Ar), 4.68 (d, *J* 6.6, 2H, CH₂OH), 4.67 (d, *J* 1.3, 2H, CH₂OTBDPS), 3.77 (t, *J* 6.6, 1H, OH), 1.08 (s, 9H, SiC(CH₃)₃); δ_{C} (90MHz) 163.6 (s), 140.9 (s), 140.8 (d), 135.5 (d), 133.1 (s), 129.8 (d), 127.8 (d), 59.1 (t), 57.2 (t), 29.8 (q), 19.2 (s); *m/z* (EI) Found: 310.0896 ([M-*t*Bu]⁺ C₁₇H₁₆NO₃Si requires 310.0899); Found: C, 68.2; H, 7.0; N, 4.0%, C₂₁H₂₅NO₃Si requires C, 68.3; H, 7.4; N, 3.8%.

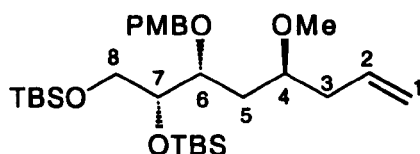
2-Bromomethyl-4-(*tert*-Butyl-diphenyl-silanyloxymethyl)-oxazole (285)



A solution of triphenylphosphine (0.18g, 0.70mmol) in dichloromethane (3ml) was added dropwise to a solution of the alcohol (284) (0.20g, 0.54mmol) and carbon tetrabromide (0.27g, 0.81mmol) in dichloromethane (10ml) at 0°C, under a nitrogen

atmosphere. The solution was stirred for 15h while allowing to warm to room temperature, the solvent was removed *in vacuo* and the residue was purified by chromatography on silica, eluting with 10% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *bromide* (0.17g, 75%) as a pale yellow oil; ν_{\max} (film) 3070, 3047, 2957, 2930, 2857, 1427, 1112, 824, 702cm⁻¹; δ_{H} (360MHz) 7.74-7.71 (m, 4H, Ar), 7.56 (t, *J* 1.0, 1H, *H*-5), 7.49-7.39 (m, 6H, Ar), 4.71 (d, *J* 1.0, 2H, CH₂OTBDPS), 4.44 (s, 2H, CH₂Br), 1.12 (s, 9H, SiC(CH₃)₃); δ_{C} (90MHz) 159.0 (s), 142.0 (s), 136.4 (d), 135.5 (d), 133.0 (s), 129.8 (d), 127.8 (d), 59.2 (t), 26.7 (q), 20.4 (t), 19.2 (s); *m/z* (FAB) Found: 428.0687 ([M-H]⁺ C₂₁H₂₃NO₂Br⁷⁹Si requires 428.0681).

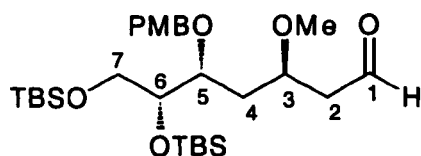
(4*S*, 6*R*, 7*R*)-7,8-bis-(*tert*-Butyl-dimethyl-silanyloxy)-4-methoxy-6-(4'-methoxy-benzyloxy)-oct-1-ene (298)



Triethylamine (1.81ml, 12.9mmol) was added in one portion to a solution of the diol (**277**) (1.00g, 3.22mmol) in dichloromethane (20ml) at 0°C, under a nitrogen atmosphere. The solution was stirred for 5min before *tert*-butyldimethylsilyl triflate (1.78ml, 7.73mmol) was added dropwise over 1min. The solution was stirred for a further 1h whilst allowing to warm to room temperature. Saturated ammonium chloride solution (40ml) was added and the organic layer was separated. The aqueous phase was extracted with dichloromethane (3 x 50ml) and the combined organic layers were dried and then concentrated *in vacuo* to leave a yellow oil. The oil was purified by chromatography on silica eluting with 10% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *silyl ether* (1.74g, 100%) as a colourless oil; $[\alpha]_{\text{D}} = +33.8$ (c = 3.0, CHCl₃); ν_{\max} (soln., CHCl₃) 1612, 1086cm⁻¹; δ_{H} (360MHz) 7.28 (d, *J* 8.7, 2H, Ar), 6.89 (d, *J* 8.7, 2H, Ar), 5.86-5.74 (m, 1H, *H*-2), 5.10-5.02 (m, 2H, *H*-1), 4.61 (d, *J* 11.3, 1H, OCHHAr), 4.48 (d, *J* 11.3, 1H, OCHHAr), 3.84-3.77 (m, 2H, *H*-7, *H*-8),

3.81 (s, 3H, ArOCH₃), 3.69 (ddd, *J* 10.5, 3.8, 2.2, 1H, *H*-6), 3.52 (dd, *J* 11.1, 7.9, 1H, *H*-8), 3.42-3.35 (m, 1H, *H*-4), 3.26 (s, 3H, OCH₃), 2.30-2.23 (m, 2H, *H*-3), 1.72 (ddd, *J* 14.4, 9.8, 2.2, 1H, *H*-5), 1.49 (ddd, *J* 14.4, 10.5, 3.0, 1H, *H*-5), 0.91 (s, 9H, SiC(CH₃)₃), 0.90 (s, 9H, SiC(CH₃)₃), 0.08 (s, 3H, SiCH₃), 0.06 (3x s, 9H, SiCH₃); δ_C (90MHz) 159.1 (s), 134.7 (d), 131.1 (s), 129.5 (d), 116.9 (t), 113.7 (d), 76.9 (d), 76.8 (d), 74.6 (d), 72.3 (t), 64.4 (t), 56.0 (q), 55.3 (q), 38.0 (t), 34.7 (t), 26.0 (q), 25.9 (q), 18.4 (s), 18.1 (s), -4.3 (q), -4.8 (q), -5.3 (q), -5.4 (q); *m/z* (EI) Found: 481.2794, ([M-*t*Bu]⁺ C₂₅H₄₅O₅Si₂ requires 481.2816); Found: C, 64.9; H, 10.3%, C₂₉H₅₄O₅Si₂ requires C, 64.6; H, 10.1%.

(3*R*, 5*R*, 6*R*)-6,7-bis-(*tert*-Butyl-dimethyl-silanyloxy)-3-methoxy-5-(4'-methoxy-benzyloxy)-heptanal (299)

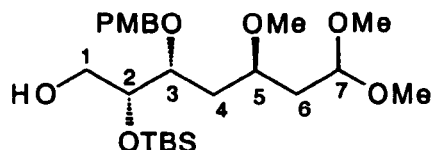


4-Methylmorpholine *N*-oxide (0.11g, 0.84mmol), followed by osmium tetroxide (20mg, cat.) were added to a solution of the silyl ether (**298**) (0.15g, 0.28mmol) in acetone (10ml) and water (1ml). The solution was stirred at room temperature for 12h and then a saturated solution of sodium thiosulfate (20ml) was added. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (30ml) and the organic phase separated. The aqueous phase was extracted with ethyl acetate (3 x 30ml) and the combined organic layers were dried (Na₂SO₄). The solvent was removed *in vacuo* to leave a colourless oil, which was used immediately without purification.

An aqueous solution of sodium periodate (85mg, 0.40mmol, 0.65M) was added dropwise over 5min to a vigorously stirred suspension of silica (1g) in dichloromethane (10ml). The crude diol in dichloromethane (5ml) was then added dropwise over 2min and the suspension stirred for 1h. The suspension was filtered and the silica was washed with dichloromethane (50ml). The solvent was removed *in*

vacuo to leave a colourless oil which was purified by chromatography on silica, eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *aldehyde* (142mg, 94%) as a colourless oil; $[\alpha]_D = +37.7$ ($c = 2.5$, CHCl_3); ν_{max} (soln., CHCl_3) 2737, 1723 cm^{-1} ; δ_{H} (360MHz) 9.77 (t, J 2.4, 1H, $H-1$), 7.26 (d, J 8.6, 2H, Ar), 6.88 (d, J 8.6, 2H, Ar), 4.61 (d, J 11.2, 1H, OCHHAr), 4.44 (d, J 11.2, 1H, OCHHAr), 3.88-3.84 (m, 1H, $H-3$), 3.81 (s, 3H, ArOCH_3), 3.82-3.77 (m, 2H, $H-6$, $H-7$), 3.63 (ddd, J 10.4, 4.2, 1.8, 1H, $H-5$), 3.51 (dd, J 10.3, 7.1, 1H, $H-7$), 3.25 (s, 3H, OCH_3), 2.58 (dd, J 5.7, 2.4, 2H, $H-2$), 1.97 (ddd, J 14.4, 8.7, 1.8, 1H, $H-4$), 1.46 (ddd, J 14.4, 10.4, 4.2, 1H, $H-4$), 0.91 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 0.90 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 0.09 (s, 3H, SiCH_3), 0.07 (s, 3H, SiCH_3), 0.06 (2x s, 6H, SiCH_3); δ_{C} (90MHz) 201.4 (d), 159.2 (s), 130.6 (s), 129.5 (d), 113.8 (d), 77.0 (d), 73.8 (d), 73.7 (d), 72.1 (t), 64.2 (t), 56.4 (q), 55.2 (q), 48.4 (t), 34.7 (t), 26.0 (q), 25.8 (q), 18.3 (s), 18.1 (s), -4.3 (q), -4.9 (q), -5.3 (q), -5.4 (q).

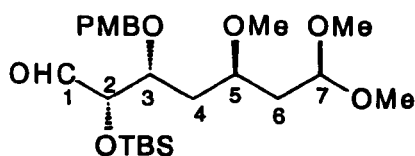
(2*R*, 3*R*, 5*R*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-5,7,7-trimethoxy-3-(4'-methoxy-benzyloxy)-heptan-1-ol (300)



10-Camphorsulfonic acid (20mg, 90 μmol) was added in one portion to a solution of the aldehyde (**299**) (95mg, 0.18mmol) in methanol (3ml) and dichloromethane (3ml) under a nitrogen atmosphere. The solution was stirred at room temperature for 1.5h, then a saturated sodium bicarbonate solution (5ml) was added and the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate (20ml) and the organic phase separated. The aqueous phase was extracted with ethyl acetate (3 x 20ml) and the combined organic layers were dried (Na_2SO_4). The solvent was removed *in vacuo* to leave a colourless oil, which was purified by chromatography on silica eluting with 30% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *alcohol* (74mg, 89%)

as a colourless oil; $[\alpha]_D = +26.0$ ($c = 2.1$, CHCl_3); ν_{max} (soln., CHCl_3) 3494, 2930, 1612, 1082 cm^{-1} ; δ_{H} (500MHz) 7.27 (d, J 8.6, 2H, Ar), 6.88 (d, J 8.6, 2H, Ar), 4.60-4.49 (m, 3H, OCH_2Ar , $H-7$), 3.94 (ddd, J 5.5, 5.5, 4.9, 1H, $H-2$), 3.81 (s, 3H, ArOCH_3), 3.79-3.68 (m, 2H, $H-1$, $H-3$), 3.60-3.55 (m, 1H, $H-1$), 3.49-3.45 (m, 1H, $H-5$), 3.33 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 3.26 (s, 3H, OCH_3), 2.25 (t, J 6.2, 1H, OH), 1.89-1.82 (m, 2H, $H-4$, $H-6$), 1.77-1.71 (m, 1H, $H-6$), 1.55 (ddd, J 14.1, 10.3, 3.5, 1H, $H-4$), 0.90 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 0.08 (2x s, 6H, SiCH_3); δ_{C} (125MHz) 159.3 (s), 130.5 (s), 129.6 (d), 113.8 (d), 102.1 (d), 77.8 (d), 74.6 (d), 72.3 (t), 71.2 (d), 63.5 (t), 59.2 (q), 55.3 (q), 52.8 (2x q), 37.5 (t), 34.3 (t), 25.8 (q), 18.0 (s), -4.7 (q), -4.8 (q); m/z (EI) Found: 351.1615, $([\text{M}-t\text{Bu}-2x\text{MeOH}]^+ \text{C}_{18}\text{H}_{27}\text{O}_5\text{Si})$ requires 351.1628; Found: C, 61.0; H, 9.7%, $\text{C}_{24}\text{H}_{44}\text{O}_7\text{Si}$ requires C, 61.0; H, 9.4%.

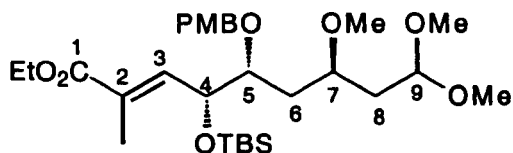
(2*S*, 3*R*, 5*R*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-5,7,7-trimethoxy-3-(4'-methoxy-benzyloxy)-heptanal (301)



2,6-Di-*tert*-butylpyridine (1.1ml, 4.8mmol) was added in one portion followed by Dess-Martin periodinane (0.68g, 1.6mmol) in one portion to a solution of the alcohol (300) (0.38g, 0.8mmol) in dichloromethane (10ml) at room temperature, under a nitrogen atmosphere. The mixture was stirred for 1h and then diethyl ether (30ml) was added and the resulting suspension poured into a saturated solution of sodium thiosulfate and sodium bicarbonate (1:1, 30ml) and stirred vigorously for 30min. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (3 x 30ml) and the combined organic layers were dried (Na_2SO_4). The solvent was removed *in vacuo* to leave a colourless oil, which was purified by chromatography on silica eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *aldehyde* (0.35g, 93%) as a colourless oil; $[\alpha]_D = +35.0$ ($c = 2.4$, CHCl_3); ν_{max} (soln., CHCl_3)

1732cm⁻¹; δ_H (360MHz) 9.71 (d, *J* 1.3, 1H, *H*-1), 7.26 (d, *J* 8.7, 2H, Ar), 6.88 (d, *J* 8.7, 2H, Ar), 4.59-4.46 (m, 3H, OCH₂Ar, *H*-7), 4.10 (dd, *J* 4.6, 1.3, 1H, *H*-2), 3.93-3.86 (m, 1H, *H*-3), 3.81 (s, 3H, ArOCH₃), 3.50-3.45 (m, 1H, *H*-5), 3.31 (2x s, 6H, OCH₃), 3.26 (s, 3H, OCH₃), 1.90-1.60 (m, 4H, *H*-4, *H*-6), 0.92 (s, 9H, SiC(CH₃)₃), 0.07 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃); δ_C (90MHz) 202.9 (d), 159.3 (s), 130.3 (s), 129.5 (d), 113.8 (d), 102.0 (d), 79.0 (d), 76.8 (d), 74.1 (d), 72.3 (t), 56.2 (q), 55.2 (q), 52.8 (q), 52.7 (q), 37.1 (t), 35.8 (t), 25.7 (q), 18.2 (s), -4.7 (q), -5.2 (q); *m/z* (EI) Found: 381.1740, ([M-*t*Bu-MeOH]⁺ C₁₉H₂₉O₆Si requires 381.1733).

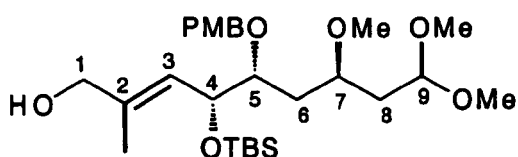
(4*R*, 5*R*, 7*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-7,9,9-trimethoxy-5-(4'-methoxy-benzyloxy)-2-methyl-non-(2*E*)-enoic acid ethyl ester (303)



(Carbethoxyethylidene)triphenylphosphorane (0.74g, 2.0mmol) was added in one portion to a solution of the aldehyde (**301**) (0.32g, 0.7mmol) in benzene (10ml) under a nitrogen atmosphere. The solution was heated at reflux for 50h, and then allowed to cool and concentrated *in vacuo*. The residue was purified by chromatography on silica eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *ester* (0.34g, 91%) as a colourless oil; $[\alpha]_D = +45.0$ (*c* = 3.3, CHCl₃); ν_{\max} (soln., CHCl₃) 1704, 1613cm⁻¹; δ_H (360MHz) 7.26 (d, *J* 8.7, 2H, Ar), 6.86 (d, *J* 8.7, 2H, Ar), 6.65 (d br q, *J* 9.1, 1.4, 1H, *H*-3), 4.70 (d, *J* 11.0, 1H, OCHHAr), 4.56-4.45 (m, 3H, OCHHAr, *H*-4, *H*-9), 4.23-4.13 (m, 2H, CH₃CH₂OCO), 3.78 (s, 3H, ArOCH₃), 3.65 (ddd, *J* 10.2, 5.4, 2.2, 1H, *H*-5), 3.50-3.44 (m, 1H, *H*-7), 3.29 (2x s, 6H, OCH₃), 3.22 (s, 3H, OCH₃), 1.85 (d, *J* 1.4, 3H, CH₃C=CH), 1.85-1.80 (m, 1H, *H*-8), 1.76-1.66 (m, 2H, *H*-6, *H*-8), 1.51 (ddd, *J* 13.8, 10.2, 3.3, 1H, *H*-6), 1.28 (t, *J* 7.1, 3H, CH₃CH₂OCO), 0.88 (s, 9H, SiC(CH₃)₃), 0.04 (s, 3H, SiCH₃), 0.00 (s, 3H,

SiCH₃); δ_C (90MHz) 167.6, (s), 159.1 (s), 140.8 (d), 130.7 (s), 129.5 (d), 128.6 (s), 113.7 (d), 101.9 (d), 79.2 (d), 74.2 (d), 73.1 (t), 71.5 (d), 60.6 (t), 55.9 (q), 55.1 (q), 52.7 (q), 52.5 (q), 37.1 (t), 35.5 (t), 25.7 (q), 18.0 (s), 14.1 (q), 13.3 (q), -4.6 (q), -4.9 (q); m/z (EI) Found: 433.2029, ([M-*t*Bu-2xMeOH]⁺ C₂₃H₃₃O₆Si requires 433.2046); Found: C, 62.8; H, 9.4%, C₂₉H₅₀O₈Si requires C, 62.8; H, 9.1%.

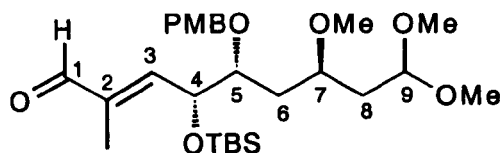
(4*R*, 5*R*, 7*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-7,9,9-trimethoxy-5-(4'-methoxy-benzyloxy)-2-methyl-non-(2*E*)-en-1-ol (304)



A solution of di-*isobutyl*aluminium hydride (0.50ml, 1M in CH₂Cl₂, 5.1mmol) was added dropwise over 5min to a stirred solution of the ester (**303**) (100mg, 1.81mmol) in dichloromethane at -78°C, under a nitrogen atmosphere. The solution was stirred at this temperature for 1h, and then allowed to warm to room temperature and stirred for a further 3h. The solution was quenched by dropwise addition of methanol (1ml) and poured into an aqueous solution of saturated potassium sodium tartrate (20ml) and stirred vigorously for 2h. The biphasic mixture was then extracted with ethyl acetate (3 x 20ml) and the combined organic extracts were dried (Na₂SO₄). The solvent was removed *in vacuo* to leave a colourless oil, which was purified by chromatography on silica eluting with ethyl acetate, to give the *alcohol* (82mg, 89%) as a colourless oil; $[\alpha]_D = +33.5$ (c = 1.9, CHCl₃); ν_{\max} (soln., CHCl₃) 3613, 3455(br) cm⁻¹; δ_H (360MHz) 7.31 (d, *J* 8.5, 2H, Ar), 6.89 (d, *J* 8.5, 2H, Ar), 5.44 (d br q, *J* 9.2, 1.2, 1H, *H*-3), 4.76 (d, *J* 11.0, 1H, OCHHAr), 4.55-4.48 (m, 3H, OCHHAr, *H*-4, *H*-9), 4.00 (s, 2H, *H*-1), 3.82 (s, 3H, ArOCH₃), 3.59 (ddd, *J* 9.7, 5.7, 1.9, 1H, *H*-5), 3.53-3.46 (m, 1H, *H*-7), 3.33 (s, 3H, OCH₃), 3.32 (s, 3H, OCH₃), 3.25 (s, 3H, OCH₃), 1.97 (br s, 1H, OH), 1.89-1.82 (m, 1H, *H*-8), 1.76-1.69 (m, 2H, *H*-6, *H*-8), 1.72 (d, *J* 1.0, 3H, CH₃C=CH), 1.51 (ddd, *J* 13.6, 10.0, 3.3, 1H, *H*-6), 0.91 (s, 9H,

SiC(CH₃)₃, 0.08 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃); δ_C (90MHz) 159.1 (s), 136.9 (s), 131.0 (s), 129.5 (d), 125.7 (d), 113.7 (d), 101.9 (d), 79.6 (d), 74.5 (d), 73.0 (t), 71.3 (d), 68.2 (t), 56.1 (q), 55.2 (q), 52.7 (q), 52.5 (q), 37.2 (t), 35.7 (t), 25.8 (q), 18.1 (s), 14.5 (q), -4.3 (q), -4.7 (q); m/z (EI) Found: 391.1946, ([M-*t*Bu-2xMeOH]⁺ C₂₁H₃₁O₅Si requires 391.1941).

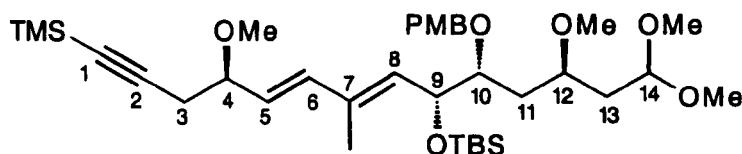
(4*R*, 5*R*, 7*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-7,9,9-trimethoxy-5-(4'-methoxy-benzyloxy)-2-methyl-non-(2*E*)-enal (305)



2,6-Lutidine (0.16ml, 1.4mmol) was added in one portion followed by Dess-Martin periodinane (0.20g, 0.47mmol) in one portion to a solution of the alcohol (**304**) (80mg, 0.16mmol) in dichloromethane (5ml) at room temperature, under a nitrogen atmosphere. The mixture was stirred for 1h and then diethyl ether (20ml) was added and the resulting suspension poured into a saturated solution of sodium thiosulfate and sodium bicarbonate (1:1, 20ml) and stirred vigorously for 30min. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (3 x 25ml) and the combined organic layers were dried (Na₂SO₄). The solvent was removed *in vacuo* to leave a colourless oil, which was purified by chromatography on silica eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *aldehyde* (75mg, 94%) as a colourless oil; $[\alpha]_D = +60.7$ (c = 1.3, CHCl₃); λ_{\max} (EtOH) 203 (8500), 217 (10100), 226 (9000), 232 (9000)nm; ν_{\max} (soln., CHCl₃) 1688cm⁻¹; δ_H (360MHz) 9.42 (s, 1H, *H*-1), 7.26 (d, *J* 8.7, 2H, Ar), 6.87 (d, *J* 8.7, 2H, Ar), 6.38 (d br q, *J* 8.6, 2.3, 1H, *H*-3), 4.71 (dd, *J* 8.6, 5.2, 1H, *H*-4), 4.67 (d, *J* 11.1, 1H, OCHHAr), 4.53 (d, *J* 11.1, 1H, OCHHAr), 4.48 (t, *J* 5.6, 1H, *H*-9), 3.80 (s, 3H, ArOCH₃), 3.72 (ddd, *J* 10.2, 5.2, 2.2, 1H, *H*-5), 3.51-3.45 (m, 1H, *H*-7), 3.31 (s, 3H, OCH₃), 3.30 (s, 3H, OCH₃), 3.24 (s, 3H, OCH₃), 1.86 (ddd, *J* 14.2, 6.1, 5.6, 1H, *H*-8),

1.76-1.68 (m, 2H, *H*-6, *H*-8), 1.77 (d, *J* 2.3, 3H, CH₃C=CH), 1.54 (ddd, *J* 13.6, 10.2, 3.2, 1H, *H*-6), 0.90 (s, 9H, SiC(CH₃)₃), 0.07 (s, 3H, SiCH₃), 0.00 (s, 3H, SiCH₃); δ_C (90MHz) 195.1 (d), 159.3 (s), 152.5 (d), 139.2 (s), 130.5 (s), 129.6 (d), 113.8 (d), 101.9 (d), 79.0 (d), 74.2 (d), 73.1 (t), 71.0 (d), 56.1 (q), 55.3 (q), 52.8 (q), 52.6 (q), 37.1 (t), 35.6 (t), 25.8 (q), 18.1 (s), 10.1 (q), -4.6 (q), -4.8 (q); *m/z* (FAB) Found: 533.2911, ([M+Na]⁺ C₂₇H₄₆O₇NaSi requires 533.2911).

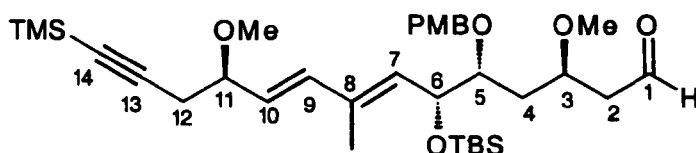
(4*R*, 9*R*, 10*R*, 12*R*)-9-(*tert*-Butyl-dimethyl-silanyloxy)-4,12,14,14-tetramethoxy-10-(4'-methoxy benzyl) -7-methyl-1-(trimethyl-silanyl)-tetradeca-di-(5*E*, 7*E*)-en-1-yne (313)



A solution of sodium *bis*(trimethylsilyl)amide (78 μ l, 1M in THF, 78 μ mol) was added dropwise to a solution of the sulfone (312) (25mg, 70 μ mol) and the aldehyde (305) (25mg, 50 μ mol) in THF (3ml) at -78°C, under a nitrogen atmosphere. The solution was stirred at -78°C for 3h and then allowed to warm up to room temperature over 1 hour. A solution of saturated ammonium chloride (5ml) was added and the organic layer was extracted with ethyl acetate (4 x 10ml). The combined organic layers were dried (Na₂SO₄) and then concentrated *in vacuo* to leave a yellow oil. The oil was purified by chromatography on silica eluting with 10% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *diene* (24mg, 74%) as a colourless oil; $[\alpha]_D = +41.3$ (c = 1.2, CHCl₃); λ_{max} (EtOH) 221 (39700), 274 (4900)nm; ν_{max} (soln., CHCl₃) 2931, 2857, 2176, 1613, 1088cm⁻¹; δ_H (360MHz) 7.29 (d, *J* 8.6, 2H, Ar), 6.88 (d, *J* 8.6, 2H, Ar), 6.25 (d, *J* 15.7, 1H, *H*-6), 5.54 (dd, *J* 15.7, 7.8, 1H, *H*-5), 5.46 (d, *J* 9.2, 1H, *H*-8), 4.76 (d, *J* 11.0, 1H, OCHHAr), 4.57 (dd, *J* 9.2, 5.8, 1H, *H*-9), 4.51 (d, *J* 11.0, 1H, OCHHAr), 4.48 (t, *J* 5.6, 1H, *H*-14), 3.81 (s, 3H, ArOCH₃), 3.77 (ddd, *J* 10.0, 5.8, 1.8, 1H, *H*-4), 3.63-3.58 (m, 1H, *H*-10), 3.50-3.46 (m, 1H, *H*-12), 3.30

(2x s, 6H, OCH₃), 3.29 (s, 3H, OCH₃), 3.23 (s, 3H, OCH₃), 2.59 (dd, *J* 16.7, 5.6, 1H, *H*-3), 2.44 (dd, *J* 16.7, 7.1, 1H, *H*-3), 1.87-1.68 (m, 3H, *H*-11, *H*-13), 1.79 (s, 3H, CH₃C=), 1.48 (ddd, *J* 13.8, 10.4, 3.3, 1H, *H*-11), 0.89 (s, 9H, SiC(CH₃)₃), 0.14 (s, 9H, Si(CH₃)₃), 0.05 (s, 3H, SiCH₃), 0.00 (s, 3H, SiCH₃); δ_C (90MHz) 159.1 (s), 137.6 (d), 133.9 (s), 133.0 (d), 131.1 (s), 129.5 (d), 127.5 (d), 113.7 (d), 103.3 (s), 102.0 (d), 86.5 (s), 80.8 (d), 79.8 (d), 74.4 (d), 73.2 (t), 71.7 (d), 56.6 (q), 56.1 (q), 55.3 (q), 52.9 (q), 52.5 (q), 37.3 (t), 35.8 (t), 27.1 (t), 25.9 (q), 18.1 (s), 13.4 (q), 0.1 (q), -4.3 (q), -4.7 (q); *m/z* (FAB) Found: 685.3972, ([M+Na]⁺ C₃₆H₆₂O₇NaSi₂ requires 685.3932).

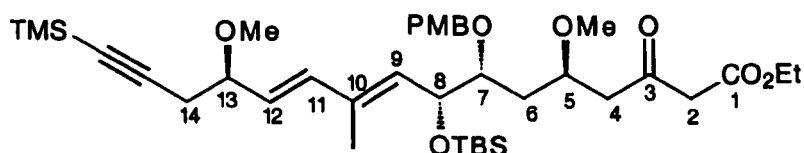
(3*R*, 5*R*, 6*R*, 11*R*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-3,11-dimethoxy-5-(4'-methoxy-benzyloxy)-8-methyl-14-(trimethyl-silanyl)-tetradeca-di-(7*E*, 9*E*)-en-13-ynal (314)



A solution of dimethylboron bromide¹³⁵ (0.61ml, 1.14M in CH₂Cl₂, 0.70mmol) was added dropwise to a solution of the dimethyl acetal (313) (58mg, 87 μ mol) in diethyl ether (5ml) at -78°C, under a nitrogen atmosphere. The solution was stirred at -78°C for 2h before being transferred *via* cannula to a vigorously stirring suspension of THF (5ml) and saturated aqueous sodium bicarbonate (5ml). The mixture was then extracted with ethyl acetate (3 x 15ml) and the combined organic layers dried (Na₂SO₄) and concentrated *in vacuo* to leave a colourless oil. The oil was purified by chromatography on silica eluting with 40% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *aldehyde* (50mg, 93%) as a colourless oil; $[\alpha]_D = +50.4$ (c = 0.9, CHCl₃); ν_{\max} (soln., CHCl₃) 1725cm⁻¹; δ_H (360MHz) 9.75 (t, *J* 2.4, 1H, *H*-1), 7.27 (d, *J* 8.6, 2H, Ar), 6.89 (d, *J* 8.6, 2H, Ar), 6.25 (d, *J* 15.7, 1H, *H*-9), 5.55 (dd, *J* 15.7, 7.8, 1H, *H*-10), 5.44 (d, *J* 9.2, 1H, *H*-7), 4.76 (d, *J* 11.1, 1H, OCHHAr), 4.62 (dd, *J* 9.2, 5.6, 1H,

H-6), 4.48 (d, *J* 11.1, 1H, OCHHAr), 3.86-3.75 (m, 2H, *H*-3, *H*-11), 3.81 (s, 3H, ArOCH₃), 3.63 (ddd, *J* 10.3, 5.6, 2.0, 1H, *H*-5) 3.31 (s, 3H, OCH₃), 3.23 (s, 3H, OCH₃), 2.63-2.55 (m, 3H, *H*-2, *H*-12), 2.44 (dd, *J* 16.7, 7.2, 1H, *H*-12), 1.87 (ddd, *J* 14.4, 9.0, 2.0, 1H, *H*-4), 1.80 (d, *J* 1.1, 3H, CH₃C=CH), 1.47 (ddd, *J* 14.4, 10.4, 3.8, 1H, *H*-4), 0.89 (s, 9H, SiC(CH₃)₃), 0.14 (s, 9H, Si(CH₃)₃), 0.06 (s, 3H, SiCH₃), 0.01 (s, 3H, SiCH₃); δ_C (90MHz) 201.4 (d), 159.3 (s), 137.4 (d), 134.3 (s), 132.4 (d), 130.6 (s), 129.6 (d), 127.7 (d), 113.8 (d), 103.3 (s), 86.5 (s), 80.7 (d), 79.5 (d), 73.2 (d), 73.1 (t), 70.9 (d), 56.7 (q), 56.3 (q), 55.3 (q), 48.3 (t), 35.6 (t), 27.1 (t), 25.8 (q), 18.1 (s), 13.4 (q), 0.1 (q), -4.3 (q), -4.8 (q).

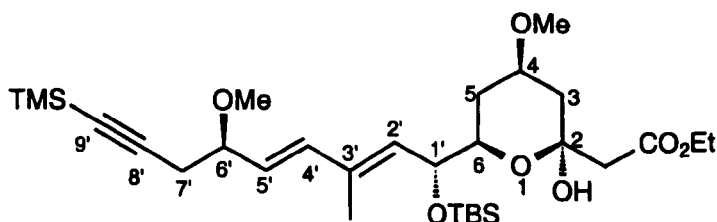
(5*R*, 7*R*, 8*R*, 13*R*)-8-(*tert*-Butyl-dimethyl-silanyloxy)-5,13-dimethoxy-7-(4'-methoxy-benzyloxy)-10-methyl-3-oxo-16-(trimethyl-silanyl)-hexadeca-di-(9*E*, 11*E*)-en-15-ynoic acid ethyl ester (315)



Ethyl diazoacetate (2.6μl, 25μmol) was added in one portion to a suspension of tin(II) chloride (0.4mg, 2μmol) in dichloromethane (1ml) at room temperature, under a nitrogen atmosphere. A solution of the aldehyde (314) (14mg, 23μmol) in dichloromethane (1ml + 1ml rinse) was then added dropwise by cannula. The suspension was stirred for 2h before being concentrated *in vacuo* to leave a yellow residue. The oil was purified by chromatography on silica eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the β-*keto ester* (12mg, 74%) as a colourless oil; [α]_D = +39.5 (c = 1.2, CHCl₃); ν_{max} (soln., CHCl₃) 1740, 1716cm⁻¹; δ_H (360MHz) 7.27 (d, *J* 8.6, 2H, Ar), 6.88 (d, *J* 8.6, 2H, Ar), 6.25 (d, *J* 15.7, 1H, *H*-11), 5.54 (dd, *J* 15.7, 7.8, 1H, *H*-12), 5.43 (d, *J* 8.9, 1H, *H*-9), 4.75 (d, *J* 11.0, 1H, OCHHAr), 4.60 (dd, *J* 9.2, 5.6, 1H, *H*-8), 4.48 (d, *J* 11.0, 1H, OCHHAr), 4.18 (q, *J* 7.1, 2H, CO₂CH₂), 3.86-3.74 (m, 2H, *H*-5, *H*-13), 3.81 (s, 3H, ArOCH₃), 3.58

(ddd, J 10.0, 5.5, 1.8, 1H, H -7), 3.42 (s, 2H, H -2) 3.31 (s, 3H, OCH_3), 3.21 (s, 3H, OCH_3), 2.74 (dd, J 16.1, 7.1, 1H, H -4), 2.63 (dd, J 16.1, 9.7, 1H, H -4), 2.59 (dd, J 16.7, 5.6, 1H, H -14), 2.44 (dd, J 16.7, 7.1, 1H, H -14), 1.81-1.73 (m, 1H, H -6), 1.79 (d, J 1.0, 3H, $\text{CH}_3\text{C}=\text{CH}$), 1.44 (ddd, J 14.5, 10.3, 4.3, 1H, H -6), 1.27 (t, J 7.1, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 0.88 (s, 9H, $\text{Si}(\text{CH}_3)_3$), 0.14 (s, 9H, $\text{Si}(\text{CH}_3)_3$), 0.05 (s, 3H, SiCH_3), 0.00 (s, 3H, SiCH_3); δ_{C} (90MHz) 201.4 (s), 167.0 (s), 159.2 (s), 137.5 (d), 134.2 (s), 132.5 (d), 130.7 (s), 129.6 (d), 127.6 (d), 113.8 (d), 103.3 (s), 86.5 (s), 80.7 (d), 79.8 (d), 74.2 (d), 72.9 (t), 71.0 (d), 61.3 (t), 56.6 (2x q), 55.3 (q), 50.0 (t), 48.1 (t), 35.3 (t), 27.1 (t), 25.8 (q), 18.1 (s), 14.1 (q), 13.4 (q), 0.1 (q), -4.3 (q), -4.8 (q); m/z (FAB) Found: 725.3815, $([\text{M}+\text{Na}]^+ \text{C}_{38}\text{H}_{62}\text{O}_8\text{NaSi}_2 \text{ requires } 725.3881)$.

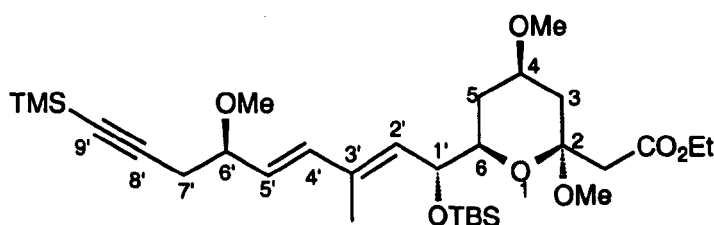
(2*R*, 4*R*, 6*R*, 1'*R*, 6'*R*)-{6-[1'-(*tert*-Butyl-dimethyl-silanyloxy)-6'-methoxy-3'-methyl-9'-(trimethyl-silyl)-nona-di-(2'*E*,4'*E*)-en-8'-ynyl]-2-hydroxy-4-methoxy-tetrahydro-pyran-2-yl}-acetic acid ethyl ester (316)



2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (10.7mg, 47 μ mol) was added in one portion to a solution of the β -keto ester (315) (22mg, 31 μ mol) in dichloromethane (4ml) and water (0.3ml) at room temperature. The solution was stirred for 2h before addition of a saturated solution of sodium bicarbonate (0.1ml). The suspension was filtered through a small pad of Celite and the solid residue washed with dichloromethane (50ml). The solvent was removed *in vacuo* and the residual oil was purified by chromatography on silica eluting with 10% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *hemi-acetal* (16mg, 88%) as a colourless oil; $[\alpha]_{\text{D}} = +3.4$ (c

= 0.55, CHCl₃); ν_{\max} (soln., CHCl₃) 3466, 1714cm⁻¹; δ_{H} (500MHz) 6.24 (d, *J* 15.7, 1H, *H*-4'), 5.54 (dd, *J* 15.7, 7.8, 1H, *H*-5'), 5.40 (d, *J* 8.8, 1H, *H*-2'), 4.45 (dd, *J* 8.9, 6.0, 1H, *H*-1'), 4.24-4.15 (m, 2H, CO₂CH₂), 3.89 (ddd, *J* 12.0, 6.0, 2.0, 1H, *H*-6), 3.81-3.76 (m, 1H, *H*-6'), 3.72-3.67 (m, 1H, *H*-4), 3.35 (s, 3H, OCH₃), 3.33 (s, 3H, OCH₃), 2.65-2.56 (m, 3H, CH₂CO₂Et, *H*-7'), 2.45 (dd, *J* 16.8, 7.2, 1H, *H*-7'), 2.23-2.17 (m, 1H, *H*-3_{eq}), 2.06-2.00 (m, 1H, *H*-5_{eq}), 1.75 (d, *J* 1.0, 3H, CH₃C=CH), 1.29 (t, *J* 7.1, 3H, CO₂CH₂CH₃), 1.16 (ddd, *J* 11.9, 11.9, 2.4, 1H, *H*-3_{ax}), 1.05 (app. q, *J* 12.0, 1H, *H*-5_{ax}), 0.85 (s, 9H, SiC(CH₃)₃), 0.14 (s, 9H, Si(CH₃)₃), 0.02 (s, 3H, SiCH₃), -0.01 (s, 3H, SiCH₃); δ_{C} (90MHz) 172.1 (s), 137.6 (d), 134.1 (s), 132.6 (d), 127.3 (d), 103.3 (s), 96.5 (s), 86.5 (s), 80.5 (d), 73.2 (d), 73.1 (d), 71.4 (d), 60.8 (t), 56.6 (q), 55.6 (q), 44.5 (t), 40.7 (t), 32.1 (t), 26.9 (t), 25.8 (q), 18.2 (s), 14.0 (q), 13.3 (q), 0.1 (q), -4.5 (q), -4.8 (q); *m/z* (FAB) Found: 605.3347, ([M+Na]⁺ C₃₀H₅₄O₇NaSi₂ requires 605.3330).

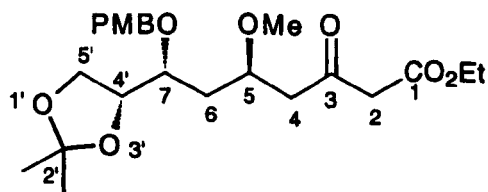
(2*R*, 4*R*, 6*R*, 1'*R*, 6'*R*)-{6-[1'-(*tert*-Butyl-dimethyl-silanyloxy)-6'-methoxy-3'-methyl-9'-(trimethyl-silanyl)-nona-di-(2'*E*,4'*E*)-en-8'-ynyl]-2,4-dimethoxy-tetrahydro-pyran-2-yl}-acetic acid ethyl ester (317)



Pyridinium *p*-toluenesulfonate (4.3mg, 17 μ mol) was added in one portion to a solution of the *hemi*-acetal (316) (10mg, 17 μ mol) in methanol (1.0ml) and dichloromethane (0.7ml) at room temperature, under a nitrogen atmosphere. The solution was stirred for 66h at this temperature before addition of a saturated solution of sodium bicarbonate (2ml). The residue was extracted with ethyl acetate (3 x 10ml), the combined extracts were then dried (Na₂SO₄) and the solvent removed *in vacuo* to leave a colourless oil.

The oil was purified by chromatography on silica eluting with 10% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *methyl ketal* (6mg, 59%) as a colourless oil; $[\alpha]_D = -30.6$ ($c = 0.24$, CHCl_3); ν_{max} (soln., CHCl_3) 1729cm^{-1} ; δ_{H} (360MHz) 6.25 (d, J 15.7, 1H, $H-4'$), 5.56 (dd, J 15.6, 7.6, 1H, $H-5'$), 5.39 (d, J 9.2, 1H, $H-2'$), 4.42 (dd, J 9.1, 7.0, 1H, $H-1'$), 4.20-4.12 (m, 2H, CO_2CH_2), 3.78 (app. q, J 7.5, 1H, $H-6'$), 3.59 (tt, J 11.0, 4.5, 1H, $H-4$), 3.47 (ddd, J 12.0, 7.0, 1.9, 1H, $H-6$), 3.33 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 3.27 (s, 3H, OCH_3), 2.83 (d, J 14.0, 1H, CHHCO_2Et), 2.60 (dd, J 17.0, 5.6, 1H, $H-7'$), 2.57 (d, J 14.0, 1H, CHHCO_2Et), 2.44 (dd, J 17.0, 7.3, 1H, $H-7'$), 2.45-2.42 (m, 1H, $H-3eq$), 1.93-1.88 (m, 1H, $H-5eq$), 1.80 (d, J 1.1, 3H, $\text{CH}_3\text{C}=\text{CH}$), 1.44 (dd, J 15.7, 11.1, 1H, $H-3ax$), 1.28 (t, J 7.1, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.04 (app. q, J 12.2, 1H, $H-5ax$), 0.87 (s, 9H, $\text{Si}(\text{CH}_3)_3$), 0.14 (s, 9H, $\text{Si}(\text{CH}_3)_3$), 0.07 (s, 3H, SiCH_3), 0.01 (s, 3H, SiCH_3); δ_{C} (90MHz) 169.1 (s), 137.3 (d), 134.2 (s), 132.2 (d), 127.8 (d), 103.2 (s), 99.4 (s), 86.6 (s), 80.7 (d), 73.4 (2x d), 72.1 (d), 60.5 (t), 56.6 (q), 55.6 (q), 47.9 (q), 42.0 (t), 39.3 (t), 32.6 (t), 27.0 (t), 25.8 (q), 18.2 (s), 14.2 (q), 13.4 (q), 0.1 (q), -4.6 (q), -4.7 (q); m/z (FAB) Found: 595.3467, $([\text{M}-\text{H}]^+ \text{C}_{31}\text{H}_{55}\text{O}_7\text{Si}_2 \text{ requires } 595.3486)$.

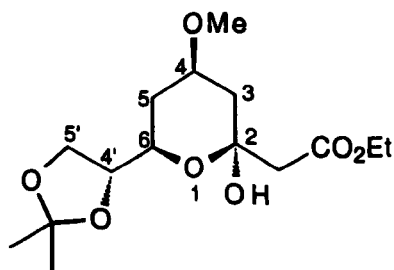
(5*R*, 7*R*, 4'*R*)-7-(2',2'-Dimethyl-[1',3']dioxolan-4'-yl)-5-methoxy-7-(4''-methoxy-benzyloxy)-3-oxo-heptanoic acid ethyl ester (319)



Ethyl diazoacetate (50 μ l, 0.48mmol) was added in one portion to a suspension of tin(II) chloride (7.5mg, 40 μ mol) in dichloromethane (6ml) at 0°C, under a nitrogen atmosphere. A solution of the aldehyde (**275**) (140mg, 0.40mmol) in dichloromethane (2ml + 1ml rinse) was then added dropwise by cannula. The suspension was allowed to warm to room temperature and stirred for 1h before addition of a saturated solution

of sodium bicarbonate (10ml). The biphasic mixture was extracted with ethyl acetate (3 x 15ml), the combined extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to leave a yellow residue. The residue was purified by chromatography on silica eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the β -keto ester (134mg, 77%) as a colourless oil; $[\alpha]_D = +42.1$ ($c = 2.4$, CHCl_3); ν_{max} (soln., CHCl_3) 1739, 1716, 1651 cm^{-1} ; δ_{H} (360MHz) 7.28 (d, J 8.6, 2H, Ar), 6.87 (d, J 8.6, 2H, Ar), 4.72 (d, J 11.2, 1H, OCHHAr), 4.51 (d, J 11.2, 1H, OCHHAr), 4.21-4.16 (m, 1H, H -5'), 4.17 (q, J 7.1, 2H, CO_2CH_2), 3.95 (dd, J 8.3, 7.6, 1H, H -5'), 3.86-3.80 (m, 1H, H -4'), 3.79 (s, 3H, ArOCH_3), 3.69-3.63 (m, 2H, H -5, H -7), 3.42 (s, 2H, $\text{CH}_2\text{CO}_2\text{Et}$), 3.22 (s, 3H, OCH_3), 2.75 (dd, J 16.3, 6.3, 1H, H -4), 2.65 (dd, J 16.3, 5.4, 1H, H -4), 1.54-1.49 (m, 2H, H -6), 1.43 (s, 3H, CCH_3), 1.35 (s, 3H, CCH_3), 1.26 (t, J 7.1, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$); δ_{C} (90MHz) 201.3 (s), 167.0 (s), 159.2 (s), 130.7 (s), 129.6 (d), 113.8 (d), 109.4 (s), 78.2 (d), 76.0 (d), 73.7 (d), 72.5 (t), 65.8 (t), 61.3 (t), 57.1 (q), 55.3 (q), 50.1 (t), 47.6 (t), 36.1 (t), 26.5 (q), 25.3 (q), 14.1 (q); m/z (EI) Found: 438.2247, (M^+ $\text{C}_{23}\text{H}_{34}\text{O}_8$ requires 438.2254); Found: C, 62.7; H, 8.0%, $\text{C}_{23}\text{H}_{34}\text{O}_8$ requires C, 63.0; H, 7.8%.

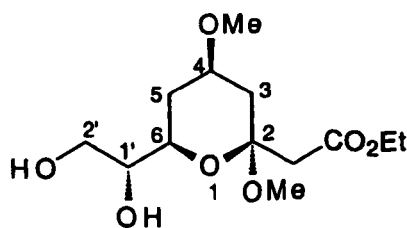
(2*S*, 4*R*, 6*R*, 4'*R*)-[[6-(2',2'-Dimethyl-[1',3']dioxolan-4'-yl)-2-hydroxy-4-methoxy-tetrahydro-pyran-2-yl]-acetic acid ethyl ester (320)



2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (22mg, 97 μmol) was added in one portion to a solution of the β -keto ester (319) (28mg, 64 μmol) in dichloromethane (3ml) and water (0.2ml) at room temperature. The solution was stirred for 2h before addition of a saturated solution of sodium bicarbonate (0.1ml). The suspension was

filtered through a small pad of Celite and the solid residue washed with dichloromethane (50ml). The filtrate was concentrated *in vacuo* and the residual oil was purified by chromatography on silica eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *hemi-acetal* (16mg, 80%) as a colourless oil; $[\alpha]_D = -20.7$ ($c = 2.5$, CHCl_3); ν_{max} (soln., CHCl_3) 3619, 3462, 1713 cm^{-1} ; δ_{H} (360MHz) 4.99 (d, J 2.5, 1H, OH), 4.25-4.09 (m, 3H, CO_2CH_2 , $H-4'$), 3.98-3.93 (m, 2H, $H-6$, $H-5'$), 3.83 (dd, J 8.2, 6.9, 1H, $H-5'$), 3.75 (app. tt, J 11.1, 4.5, 1H, $H-4$), 3.36 (s, 3H, OCH_3), 2.67 (d, J 15.3, 1H, CHHCO_2Et), 2.59 (d, J 15.3, 1H, CHHCO_2Et), 2.22 (ddd, J 11.2, 4.6, 1.8, 1H, $H-3eq$), 2.02-1.98 (m, 1H, $H-5eq$), 1.38 (s, 3H, CCH_3), 1.36 (s, 3H, CCH_3), 1.28 (t, J 7.2, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$) 1.31-1.24 (obs. m, 2H, $H-3ax$, $H-5ax$); δ_{C} (90MHz) 172.0 (s), 109.3 (s), 96.6 (s), 77.2 (d), 72.8 (d), 68.3 (d), 65.2 (t), 61.0 (t), 55.5 (q), 44.7 (t), 40.6 (t), 32.3 (t), 26.0 (q), 25.6 (q), 14.0 (q); m/z (EI) Found: 303.1439, $([\text{M}-\text{Me}]^+ \text{C}_{14}\text{H}_{23}\text{O}_7 \text{requires } 303.1444)$; Found: C, 56.6; H, 8.4%, $\text{C}_{15}\text{H}_{26}\text{O}_7 \text{requires C, 56.6; H, 8.2\%}$.

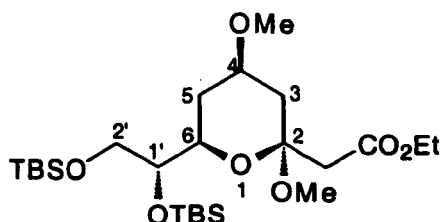
(2*S*, 4*R*, 6*R*, 1'*R*)-[6-(1',2'-Dihydroxy-ethyl)-2,4-dimethoxy-tetrahydro-pyran-2-yl]-acetic acid ethyl ester (321)



Pyridinium *p*-toluenesulfonate (26mg, 1.0mmol) was added in one portion to a solution of the *hemi-acetal* (320) (33mg, 1.0mmol) in methanol (3ml) at room temperature, under a nitrogen atmosphere. The solution was stirred for 60h at this temperature before addition of a saturated solution of sodium bicarbonate (10ml). The residue was extracted with ethyl acetate (3 x 10ml), the combined extracts were then dried (Na_2SO_4) and the solvent removed *in vacuo* to leave a colourless oil. The oil was purified by chromatography on silica eluting with 50% ethyl acetate in petroleum ether (b.p. 40-

60°C) increasing to 100% ethyl acetate, to give the *methyl ketal* (24mg, 79%) as a colourless oil; $[\alpha]_D = -65.6$ ($c = 1.4$, CHCl_3); ν_{max} (soln., CHCl_3) 3573, 1726, 1084 cm^{-1} ; δ_{H} (360MHz) 4.11 (q, J 7.1, 2H, CO_2CH_2), 3.70-3.57 (m, 5H, $H-4$, $H-6$, $H-1'$, $H-2'$), 3.30 (s, 3H, OCH_3), 3.24 (br s, 1H, OH), 3.19 (s, 3H, OCH_3), 2.95 (br s, 1H, OH), 2.70 (d, J 13.7, 1H, CHHCO_2Et), 2.62 (d, J 13.7, 1H, CHHCO_2Et), 2.31 (ddd, J 12.8, 4.5, 1.7, 1H, $H-3_{\text{eq}}$), 1.97-1.92 (m, 1H, $H-5_{\text{eq}}$), 1.42 (dd, J 12.7, 11.1, 1H, $H-3_{\text{ax}}$), 1.30 (app. q, J 11.7, 1H, $H-5_{\text{ax}}$), 1.23 (t, J 7.1, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$); δ_{C} (90MHz) 169.1 (s), 99.5 (s), 73.7 (d), 72.6 (d), 70.3 (d), 63.3 (t), 60.7 (t), 55.5 (q), 48.0 (q), 41.9 (t), 39.1 (t), 32.4 (t), 14.0 (q); m/z (EI) Found: 231.1235, $([\text{M}-\text{C}_2\text{H}_5\text{O}_2]^+ \text{C}_{11}\text{H}_{19}\text{O}_5 \text{ requires } 231.1233)$.

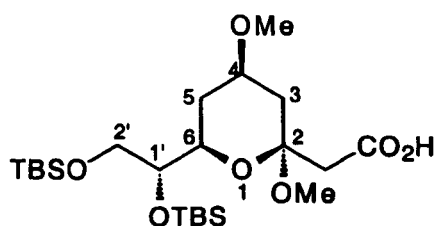
(2*S*, 4*R*, 6*R*, 1'*R*)-{6-[1',2'-bis-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-2,4-dimethoxy-tetrahydro-pyran-2-yl}-acetic acid ethyl ester (323)



Triethylamine (0.70ml, 5.0mmol) was added in one portion to a solution of the diol (321) (0.29g, 1.0mmol) in dichloromethane (10ml) at 0°C, under a nitrogen atmosphere. The solution was stirred for 10min before *tert*-butyldimethylsilyl triflate (0.50ml, 2.2mmol) was added dropwise over 1min. The solution was stirred for a further 30min at 0°C, before a saturated solution of ammonium chloride (10ml) was added and the organic layer was separated. The aqueous phase was extracted with dichloromethane (3 x 20ml) and the combined organic layers were dried and then concentrated *in vacuo* to leave a colourless oil. The oil was purified by chromatography on silica eluting with 10% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *silyl ether* (0.42g, 82%) as a colourless oil; $[\alpha]_D = -37.5$ ($c = 1.1$, CHCl_3); ν_{max} (soln., CHCl_3) 2931, 2857, 1730, 1463, 1370, 1315, 1085 cm^{-1} ; δ_{H} (360MHz) 4.18-

4.10 (m, 2H, CO₂CH₂), 3.71 (dd, *J* 9.6, 4.4, 1H, *H*-2'), 3.67-3.53 (m, 4H, *H*-4, *H*-6, *H*-1', *H*-2'), 3.34 (s, 3H, OCH₃), 3.24 (s, 3H, OCH₃), 2.79 (d, *J* 13.8, 1H, CHHCO₂Et), 2.57 (d, *J* 13.7, 1H, CHHCO₂Et), 2.38 (ddd, *J* 12.7, 4.6, 1.9, 1H, *H*-3_{eq}), 2.03-1.98 (m, 1H, *H*-5_{eq}), 1.46 (dd, *J* 12.7, 11.1, 1H, *H*-3_{ax}), 1.26 (t, *J* 7.1, 3H, CO₂CH₂CH₃), 1.19 (app. q, *J* 11.7, 1H, *H*-5_{ax}), 0.89 (2x s, 18H, SiC(CH₃)₃), 0.07 (2x s, 6H, SiCH₃), 0.04 (s, 6H, Si(CH₃)₂); δ_C (90MHz) 169.1 (s), 99.4 (s), 75.2 (d), 73.5 (d), 70.2 (d), 64.3 (t), 60.5 (t), 55.5 (q), 47.9 (q), 42.0 (t), 39.5 (t), 32.3 (t), 25.9 (2x q), 18.3 (s), 18.1 (s), 14.1 (q), -4.4 (q), -4.6 (q), -5.4 (2x q); *m/z* (FAB) Found: 543.3172, ([M+Na]⁺ C₂₅H₅₂O₇Si₂Na requires 543.3149); Found: C, 57.8; H, 10.4%, C₂₅H₅₂O₇Si₂ requires C, 57.7; H, 10.1%.

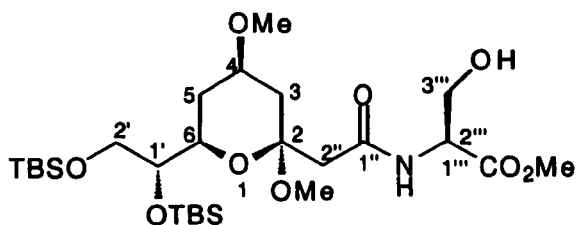
(2*S*, 4*R*, 6*R*, 1'*R*)-{6-[1',2'-bis-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-2,4-dimethoxy-tetrahydro-pyran-2-yl}-acetic acid (324)



Lithium hydroxide monohydrate (109mg, 2.59mmol) was added in one portion to a solution of the ester (323) (135mg, 0.26mmol) in methanol (3ml) and water (1ml) at room temperature and stirred vigorously for 16h. The solution was neutralised by addition of 10% citric acid solution (5ml) and then extracted with ethyl acetate (3 x 15ml), the combined extracts were then dried (Na₂SO₄) and concentrated *in vacuo* to leave the crude acid as a colorless oil, which was used without further purification; [α]_D = -82.5 (c = 0.9, CHCl₃); ν_{max} (soln., CHCl₃) 3216, 1746cm⁻¹; δ_H (360MHz) 3.97 (br d, *J* 12.2, 1H, *H*-2'), 3.77-3.68 (m, 2H, *H*-1', *H*-2'), 3.61-3.54 (m, 2H, *H*-4, *H*-6), 3.36 (s, 3H, OCH₃), 3.24 (s, 3H, OCH₃), 2.98 (d, *J* 15.2, 1H, CHHCO₂H), 2.57 (d, *J* 15.2, 1H, CHHCO₂H), 2.29 (ddd, *J* 12.8, 4.4, 1.7, 1H, *H*-3_{eq}), 1.91-1.86 (m, 1H, *H*-5_{eq}), 1.49 (app. q, *J* 12.1, 1H, *H*-5_{ax}), 1.40 (dd, *J* 12.8, 11.0, 1H,

H-3 α), 0.90 (s, 9H, SiC(CH₃)₃), 0.89 (s, 9H, SiC(CH₃)₃), 0.10 (s, 3H, SiCH₃), 0.08 (s, 3H, SiCH₃), 0.06 (s, 3H, SiCH₃), 0.05 (s, 3H, SiCH₃); δ_C (90MHz) 171.6 (s), 99.1 (s), 74.5 (d), 72.9 (d), 69.4 (d), 63.2 (t), 55.5 (q), 48.0 (q), 41.9 (t), 38.9 (t), 32.6 (t), 25.8 (q), 25.7 (q), 18.2 (s), 18.0 (s), -4.5 (q), -4.7 (q), -5.4 (q), -5.5 (q); *m/z* (FAB) Found: 515.2864, ([M+Na]⁺ C₂₃H₄₈O₇Si₂Na requires 515.2836).

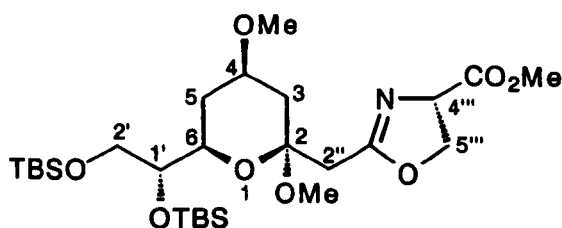
(2*S*, 4*R*, 6*R*, 1'*R*, 2'''*S*)-2''-(2-{6-[1',2'-bis-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-2,4-dimethoxy-tetrahydro-pyran-2-yl}-acetyl-amino)-3'''-hydroxy-propionic acid methyl ester (325)



Triethylamine (0.29ml, 2.1mmol) was added in one portion to a suspension of *l*-serine methyl ester hydrochloride (81mg, 0.52mmol) in THF (5ml) at 0°C, under a nitrogen atmosphere and stirred for 30min. The crude acid (324) in THF (5ml) was then added, followed by sequential addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (149mg, 0.78mmol) and 1-hydroxybenzotriazole (88mg, 0.65mmol). The solution was stirred at 0°C for 1h before allowing to warm to room temperature over a further 1h. A saturated ammonium chloride solution (10ml) was added and the solvent was removed *in vacuo*. The residue was extracted with ethyl acetate (4 x 15ml), the combined extracts were then dried (Na₂SO₄) and concentrated *in vacuo* to leave a yellow residue. The residue was purified by chromatography on silica, eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *hydroxy-amide* (113mg, 73%, 2 steps) as a colourless oil; $[\alpha]_D = -32.7$ (c = 4.6, CHCl₃); ν_{\max} (soln., CHCl₃) 3626, 3360, 1746, 1667cm⁻¹; δ_H (360MHz) 7.37 (d, *J* 7.6, 1H, NH), 4.58 (dt, *J* 7.5, 3.7, 1H, *H*-2'''), 3.99-3.88 (m, 2H, *H*-3'''), 3.81-3.65 (m, 4H, *H*-4, *H*-6, *H*-1', *H*-2'), 3.78 (s, 3H, OCH₃), 3.60 (dd, *J* 9.8, 4.7, 1H, *H*-2'), 3.34 (s, 3H,

OCH₃), 3.25 (s, 3H, OCH₃), 3.06-2.98 (br m, 1H, OH), 2.85 (d, *J* 14.7, 1H, CHHCO₂NH), 2.52 (d, *J* 14.7, 1H, CHHCO₂NH), 2.28 (ddd, *J* 12.7, 4.6, 1.5, 1H, *H*-3_{eq}), 1.99-1.95 (m, 1H, *H*-5_{eq}), 1.47 (dd, *J* 12.7, 11.1, 1H, *H*-3_{ax}), 1.30 (app. q, *J* 12.0, 1H, *H*-5_{ax}), 0.90 (s, 9H, SiC(CH₃)₃), 0.89 (s, 9H, SiC(CH₃)₃), 0.10 (s, 6H, Si(CH₃)₂), 0.06 (s, 6H, SiCH₃); δ_C (90MHz) 170.7 (s), 169.5 (s), 99.5 (s), 75.3 (d), 73.3 (d), 70.2 (d), 63.9 (t), 63.1 (t), 55.5 (q), 54.7 (d), 52.5 (q), 47.9 (q), 43.7 (t), 38.2 (t), 32.6 (t), 25.9 (2x q), 18.2 (s), -4.5 (q), -4.6 (q), -5.4 (2x q); *m/z* (FAB) Found: 616.3306, ([M+Na]⁺ C₂₇H₅₅O₉NSi₂Na requires 616.3313).

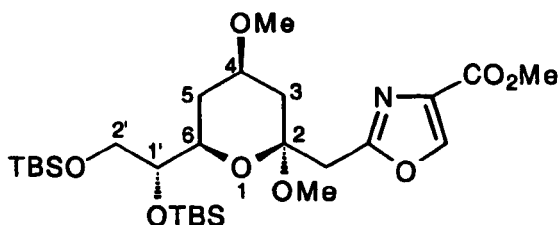
(2*S*, 4*R*, 6*R*, 1'*R*, 4*S*)-2''-{6-[1',2'-bis-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-2,4-dimethoxy-tetrahydro-pyran-2-ylmethyl}-4,5-dihydro-oxazole-4-carboxylic acid methyl ester (326)



Diethylaminosulfur trifluoride (26μl, 0.20mmol) was added dropwise to a solution of the hydroxy-amide (325) (83mg, 0.14mmol) in dichloromethane (2ml) at -78°C, under a nitrogen atmosphere. The solution was stirred at -78°C for 1h before addition of a solution of ammonium hydroxide (5ml, 4M) and ice (10g). The biphasic mixture was allowed to warm to room temperature and then extracted with dichloromethane (3 x 20ml), the combined extracts were then dried (Na₂SO₄) and concentrated *in vacuo* to leave a yellow oil. The oil was purified by chromatography on silica, eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *oxazoline* (64mg, 80%) as a colourless oil; [α]_D = +12.6 (c = 2.7, CHCl₃); ν_{max} (soln., CHCl₃) 2930, 2885, 2857, 1742, 1658, 1462, 1362, 1084, 992cm⁻¹; δ_H (360MHz) 4.73 (dd, *J* 10.7, 7.8, 1H, *H*-4''), 4.49 (dd, *J* 8.7, 7.8, 1H, *H*-5''), 4.40 (dd, *J* 10.7, 8.8, 1H, *H*-5''), 3.77 (s, 3H, OCH₃), 3.75-3.52 (m, 5H, *H*-4, *H*-6, *H*-1', *H*-2'), 3.33 (s, 3H, OCH₃), 3.25 (s,

3H, OCH₃), 2.96 (d, *J* 14.4, 1H, CHHO_x), 2.55 (d, *J* 14.4, 1H, CHHO_x), 2.37 (ddd, *J* 12.7, 4.5, 1.7, 1H, *H*-3_{eq}), 2.01-1.97 (m, 1H, *H*-5_{eq}), 1.36 (dd, *J* 12.7, 11.2, 1H, *H*-3_{ax}), 1.30 (app. q, *J* 11.6, 1H, *H*-5_{ax}), 0.88 (2x s, 18H, SiC(CH₃)₃), 0.06 (s, 6H, Si(CH₃)₂), 0.03 (s, 6H, Si(CH₃)₂); δ_C (90MHz) 171.5 (s), 166.5 (s), 99.4 (s), 75.1 (d), 73.5 (d), 70.3 (d), 69.5 (t), 67.9 (d), 64.3 (t), 55.4 (q), 52.6 (q), 47.9 (q), 39.5 (t), 35.7 (t), 32.3 (t), 25.9 (q), 25.8 (q), 18.3 (s), 18.1 (s), -4.4 (q), -4.7 (q), -5.4 (2x q); *m/z* (FAB) Found: 598.3165, ([M+Na]⁺ C₂₇H₅₃O₈NSi₂Na requires 598.3207).

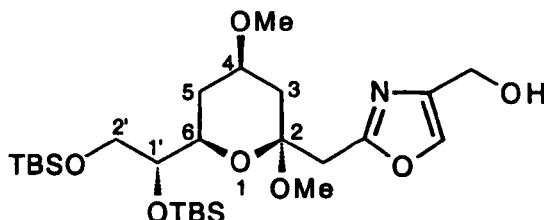
(2*S*, 4*R*, 6*R*, 1'*R*)-2''-{6-[1',2'-bis-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-2,4-dimethoxy-tetrahydro-pyran-2-ylmethyl}-oxazole-4''-carboxylic acid methyl ester (327)



1,8-Diazabicyclo[5.4.0]undec-7-ene (17μl, 0.12mmol) was added in one portion to a solution of the oxazoline (326) (61mg, 0.11mmol) in dichloromethane (5ml) at 0°C, under a nitrogen atmosphere. Bromotrichloromethane (12μl, 0.12mmol) was then added dropwise and the solution was stirred for 14h whilst allowing to warm to room temperature. A saturated ammonium chloride solution (5ml) was added and the organics were extracted with ethyl acetate (3 x 15ml), the combined extracts were then dried (Na₂SO₄) and concentrated *in vacuo* to leave a yellow residue. The residue was purified by chromatography on silica, eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *oxazole* (50mg, 82%) as a colourless oil; [α]_D = -30.9 (c = 2.8, CHCl₃); ν_{max} (soln., CHCl₃) 2929, 2885, 2857, 1739, 1586, 1462, 1381, 1360, 1324, 1083cm⁻¹; δ_H (360MHz) 8.17 (s, 1H, Ox-*H*), 3.91 (s, 3H, OCH₃), 3.73-3.51 (m, 5H, *H*-4, *H*-6, *H*-1', *H*-2'), 3.32 (s, 6H, OCH₃), 3.29 (d, *J* 14.7, 1H, CHHO_x),

3.14 (d, J 14.7, 1H, CHHOx), 2.20 (ddd, J 12.6, 4.5, 1.6, 1H, H -3 eq), 2.00-1.95 (m, 1H, H -5 eq), 1.43 (dd, J 12.6, 11.1, 1H, H -3 ax), 1.18 (app. q, J 11.9, 1H, H -5 ax), 0.89 (s, 9H, SiC(CH₃)₃), 0.88 (s, 9H, SiC(CH₃)₃), 0.07 (2x s, 6H, SiCH₃), 0.05 (s, 6H, Si(CH₃)₂); δ_C (90MHz) 161.6 (s), 161.3 (s), 144.3 (d), 133.3 (s), 99.6 (s), 75.0 (d), 73.5 (d), 70.3 (d), 64.1 (t), 55.5 (q), 52.1 (q), 48.0 (q), 39.3 (t), 35.7 (t), 32.2 (t), 25.9 (q), 25.8 (q), 18.3 (s), 18.1 (s), -4.4 (q), -4.7 (q), -5.4 (2x q); m/z (FAB) Found: 596.3058, ([M+Na]⁺ C₂₇H₅₁NO₈Si₂Na requires 596.3051).

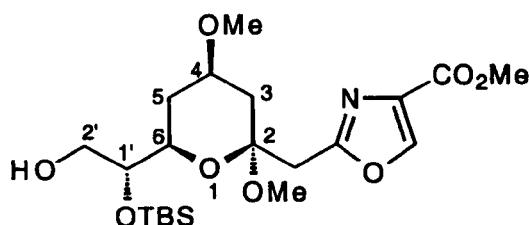
(2*S*, 4*R*, 6*R*, 1'*R*)-(2''-{6-[1',2'-bis-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-2,4-dimethoxy-tetrahydro-pyran-2-ylmethyl}-oxazol-4''-yl)-methanol (328)



A solution of di-*isobutyl*aluminium hydride (0.11ml, 1.5M in toluene, 0.17mmol) was added dropwise to a solution of the ester (327) (40mg, 70 μ mol) in dichloromethane (3ml) at -78°C, under a nitrogen atmosphere. The solution was stirred at -78°C for 1h and then at room temperature for a further 1h, before dropwise addition of methanol (0.5ml). The resultant suspension was then poured into a saturated solution of potassium sodium tartrate (10ml) and stirred vigorously for 1h. The organics were extracted with ethyl acetate (3 x 15ml), the combined extracts were then dried (Na₂SO₄) and concentrated *in vacuo* to leave a colourless oil. The oil was purified by chromatography on silica, eluting with 70% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *alcohol* (33mg, 87%) as a colourless oil; $[\alpha]_D = -28.6$ ($c = 1.6$, CHCl₃); ν_{max} (soln., CHCl₃) 3606, 1571, 1386, 1083cm⁻¹; δ_H (360MHz) 7.52 (t, J 0.9, 1H, Ox-H), 4.58 (br d, J 4.3, 2H, CH₂OH), 3.73 (dd, J 9.8, 4.9, 1H, H -2'), 3.69-3.53 (m, 4H, H -4, H -6, H -1', H -2'), 3.33 (s, 3H, OCH₃), 3.32 (s, 3H, OCH₃), 3.26 (d, J 14.8, 1H, CHHOx), 3.03 (d, J 14.8, 1H, CHHOx), 2.26 (br t, J 4.3, 1H,

OH), 2.22 (ddd, J 12.7, 4.6, 1.7, 1H, H -3 eq), 2.02-1.98 (m, 1H, H -5 eq), 1.41 (dd, J 12.6, 11.1, 1H, H -3 ax), 1.18 (app. q, J 11.9, 1H, H -5 ax), 0.90 (s, 18H, $\text{SiC}(\text{CH}_3)_3$), 0.09 (s, 3H, SiCH_3), 0.08 (s, 3H, SiCH_3), 0.06 (s, 6H, $\text{Si}(\text{CH}_3)_2$); δ_{C} (90MHz) 160.7 (s), 140.2 (s), 135.2 (d), 99.7 (s), 75.1 (d), 73.6 (d), 70.3 (d), 64.3 (t), 56.9 (t), 55.5 (q), 47.9 (q), 39.3 (t), 35.7 (t), 32.2 (t), 25.9 (2x q), 18.3 (s), 18.1 (s), -4.4 (q), -4.7 (q), -5.4 (2x q).

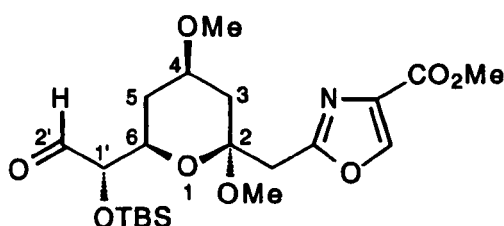
(2*S*, 4*R*, 6*R*, 1'*R*)-2''-{6-[1'-(*tert*-Butyl-dimethyl-silanyloxy)-2'-hydroxy-ethyl]-2,4-dimethoxy-tetrahydro-pyran-2-ylmethyl}-oxazole-4''-carboxylic acid methyl ester (330)



10-Camphorsulfonic acid (15mg, 66 μ mol) was added in one portion to a solution of the *bis*-silyl ether (327) (76mg, 0.13mmol) in methanol (2ml) and dichloromethane (4ml) at 0°C, under a nitrogen atmosphere. The solution was stirred at 0°C for 2h and then at room temperature for a further 4h. A saturated sodium bicarbonate solution (2ml) was added and the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate (10ml) and the organic phase separated. The aqueous phase was extracted with ethyl acetate (3 x 10ml) and the combined organic layers were dried (Na_2SO_4) and the solvent removed *in vacuo* to leave a colourless oil. The oil was purified by chromatography on silica eluting with 50% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *alcohol* (36mg, 59%) as a colourless oil; $[\alpha]_{\text{D}} = -16.9$ ($c = 1.8$, CHCl_3); ν_{max} (soln., CHCl_3) 3565 (br), 1739, 1586, 1325, 1111, 1084 cm^{-1} ; δ_{H} (360MHz) 8.19 (s, 1H, Ox-H), 3.91 (s, 3H, OCH_3), 3.76-3.56 (m, 5H, H -4, H -6, H -1', H -2'), 3.33 (s, 3H, OCH_3), 3.31 (s, 3H, OCH_3), 3.30 (d, J 14.7, 1H, CHHOx), 3.13 (d, J 14.7, 1H, CHHOx), 2.24-2.02 (m, 3H, OH , H -3 eq , H -5 eq),

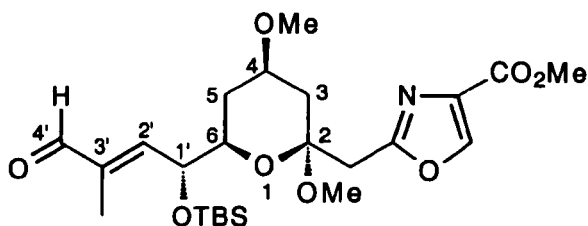
1.40 (dd, J 12.6, 11.2, 1H, H -3 ax), 1.12 (app. q, J 11.5, 1H, H -5 ax), 0.91 (s, 9H, SiC(CH₃)₃), 0.13 (s, 3H, SiCH₃), 0.11 (s, 3H, SiCH₃); δ_C (90MHz) 161.4 (s), 160.9 (s), 144.3 (d), 133.3 (s), 99.7 (s), 74.0 (d), 73.0 (d), 71.4 (d), 63.5 (t), 55.6 (q), 53.1 (q), 48.1 (q), 39.2 (t), 35.6 (t), 31.8 (t), 25.8 (q), 18.0 (s), -4.5 (q), -4.8 (q); m/z (FAB) Found: 460.2355, ([MH]⁺ C₂₁H₃₈NO₈Si requires 460.2367).

(2*S*, 4*R*, 6*R*, 1'*R*)-2''-{6-[1'-(*tert*-Butyl-dimethyl-silanyloxy)-2'-oxo-ethyl]-2,4-dimethoxy-tetrahydro-pyran-2-ylmethyl}-oxazole-4''-carboxylic acid methyl ester (331)



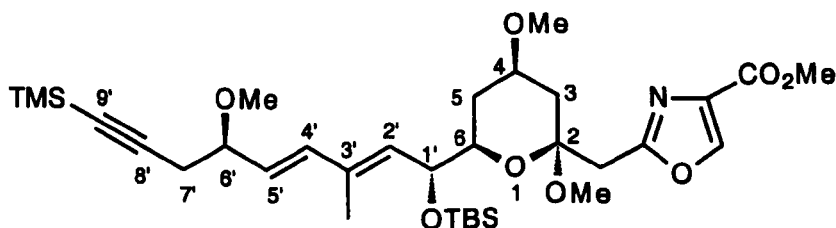
2,6-Di-*tert*-butyl-4-methyl-pyridine (91mg, 0.44mmol), followed by Dess-Martin periodinane (63mg, 0.15mmol) were added in one portion to a solution of the alcohol (**330**) (34mg, 74 μ mol) in dichloromethane (5ml) at room temperature, under a nitrogen atmosphere. The mixture was stirred for 4h and then diethyl ether (20ml) was added and the resulting suspension poured into a saturated solution of sodium thiosulfate and sodium bicarbonate (1:1, 20ml) and stirred vigorously for 30min. The organic layer was separated, the aqueous phase was extracted with ethyl acetate (3 x 15ml) and the combined organic layers were dried (Na₂SO₄). The solvent was removed *in vacuo* to leave a colourless oil, which was purified by chromatography on silica eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *aldehyde* (28mg, 83%) as a colourless oil; δ_H (360MHz) 9.68 (s, 1H, H -2'), 8.17 (s, 1H, Ox- H), 3.94 (br s, 2H, H -6, H -1'), 3.91 (s, 3H, OCH₃), 3.86-3.82 (m, 1H, H -4), 3.31 (s, 3H, OCH₃), 3.24 (s, 3H, OCH₃), 3.22 (d, J 14.8, 1H, CHHOx), 3.13 (d, J 14.8, 1H, CHHOx), 2.22-2.17 (m, 1H, H -3 eq), 1.91-1.86 (m, 1H, H -5 eq), 1.48-1.32 (m, 2H, H -3 ax , H -5 ax), 0.92 (s, 9H, SiC(CH₃)₃), 0.08 (s, 3H, SiCH₃), 0.07 (s, 3H, SiCH₃).

(2*S*, 4*R*, 6*R*, 1'*R*)-2''-{6-[1'-(*tert*-Butyl-dimethyl-silanyloxy)-3'-methoxy-4'-oxo-but-(2'*E*)-enyl]-2,4-dimethoxy-tetrahydro-pyran-2-ylmethyl}-oxazole-4''-carboxylic acid methyl ester (332)



2-(Triphenylphosphoranylidene)-propionaldehyde (**262**) (22mg, 68 μ mol) was added in one portion to a solution of the aldehyde (**331**) (26mg, 57 μ mol) in benzene (4ml) under a argon atmosphere. The solution was heated at reflux for 96h and then cooled and concentrated *in vacuo*. The residue was purified by chromatography on silica eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the crude *aldehyde* (7mg, 25%) as a colourless oil, which was used without charcaterisation.

(2*S*, 4*R*, 6*R*, 1'*R*, 6'*R*)-2''-{6-[1'-(*tert*-Butyl-dimethyl-silanyloxy)-6'-methoxy-3'-methyl-9'-(trimethyl-silanyl)-nona-di-(2'*E*,4'*E*)-en-8'-ynyl]-2,4-dimethoxy-tetrahydro-pyran-2-ylmethyl}-oxazole-4''-carboxylic acid methyl ester (333)



A solution of sodium *bis*(trimethylsilyl)amide (28 μ l, 1M in THF, 28 μ mol) was added dropwise to a solution of the sulfone (**312**) (10mg, 28 μ mol) and the aldehyde (**332**) (5mg, 10 μ mol) in THF (1.5ml) at -78°C, under a argon atmosphere. The solution was stirred at -78°C for 3h and then a solution of saturated ammonium chloride (1ml) was

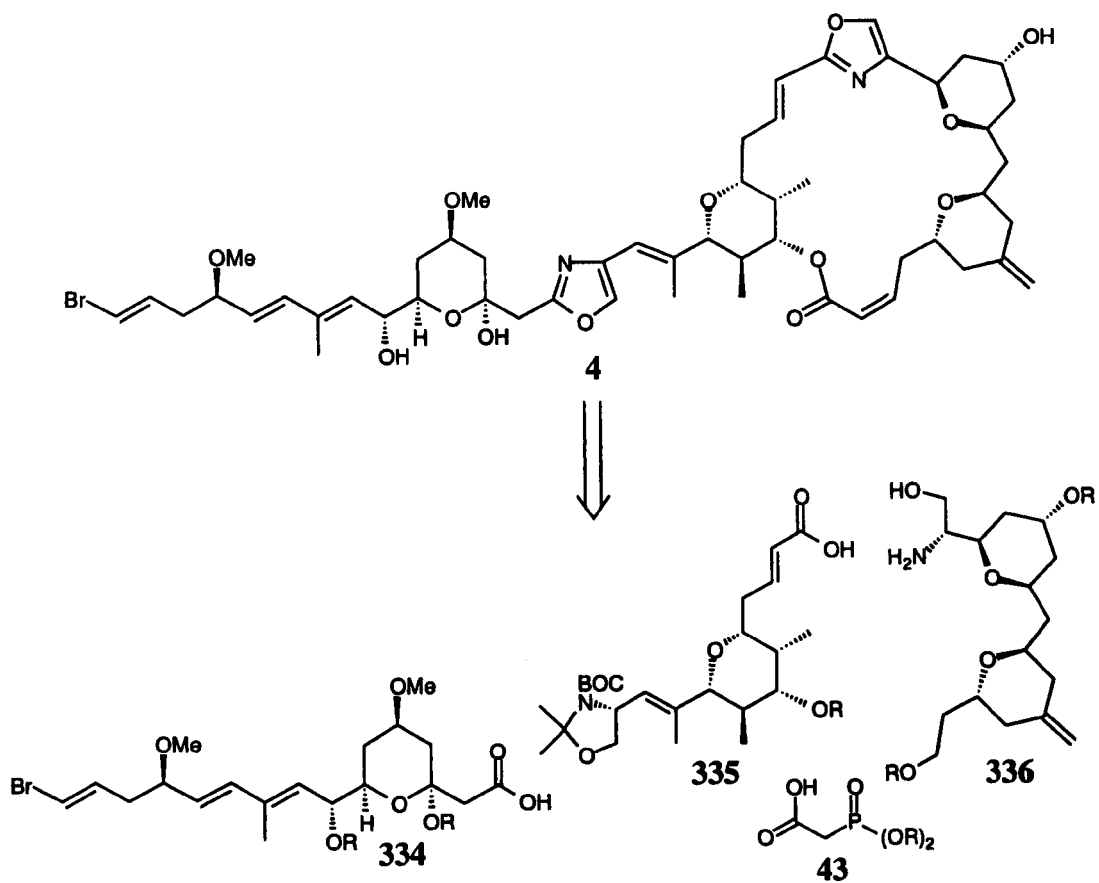
added, and the suspension allowed to warm to room temperature. The organic layer was extracted with ethyl acetate (3 x 10ml) and the combined organic layers were dried (Na_2SO_4) and then concentrated *in vacuo* to leave a colourless oil. The oil was purified by chromatography on silica eluting with 20% ethyl acetate in petroleum ether (b.p. 40-60°C), to give the *diene* (3.8mg, 59%) as a colourless oil; δ_{H} (500MHz) 8.19 (s, 1H, Ox-H), 6.26 (d, J 15.7, 1H, $H-4'$), 5.59 (dd, J 15.7, 7.5, 1H, $H-5'$), 5.44 (d, J 8.4, 1H, $H-2'$), 4.48 (dd, J 8.4, 4.7, 1H, $H-1'$), 3.92 (s, 3H, OCH_3), 3.80 (app. q, J 6.7, 1H, $H-6'$), 3.59-3.55 (m, 1H, $H-4$), 3.46-3.43 (m, 1H, $H-6$), 3.34 (s, 3H, OCH_3), 3.31 (s, 3H, OCH_3), 3.30 (d, J 15.0, 1H, CHHOx), 3.26 (s, 3H, OCH_3), 3.06 (d, J 15.0, 1H, CHHOx), 2.60 (dd, J 16.8, 5.6, 1H, $H-7'$), 2.46 (dd, J 16.8, 6.8, 1H, $H-7'$), 2.21-2.17 (m, 1H, $H-3eq$), 2.08-2.05 (m, 1H, $H-5eq$), 1.80 (s, 3H, $\text{CH}_3\text{C}=\text{CH}$), 1.42 (app. t, J 11.8, 1H, $H-3ax$), 1.28-1.24 (m, 1H, $H-5ax$), 0.88 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 0.14 (s, 9H, $\text{Si}(\text{CH}_3)_3$), 0.05 (s, 3H, SiCH_3), 0.02 (s, 3H, SiCH_3); δ_{C} (125MHz) 161.6 (s), 161.1 (s), 144.3 (d), 137.0 (d), 133.8 (s), 133.3 (s), 133.2 (d), 127.4 (d), 103.3 (s), 99.7 (s), 86.6 (s), 80.5 (d), 73.4 (d), 73.3 (d), 71.6 (d), 56.6 (q), 55.6 (q), 52.1 (q), 47.9 (q), 39.4 (t), 35.8 (t), 31.6 (t), 27.0 (t), 25.8 (q), 18.2 (s), 13.2 (q), 0.1 (q), -4.4 (q), -4.8 (q); m/z (FAB) Found: 672.3316, ($[\text{M}+\text{Na}]^+$ $\text{C}_{33}\text{H}_{55}\text{NO}_8\text{Si}_2\text{Na}$ requires 672.3364).

4. APPENDIX

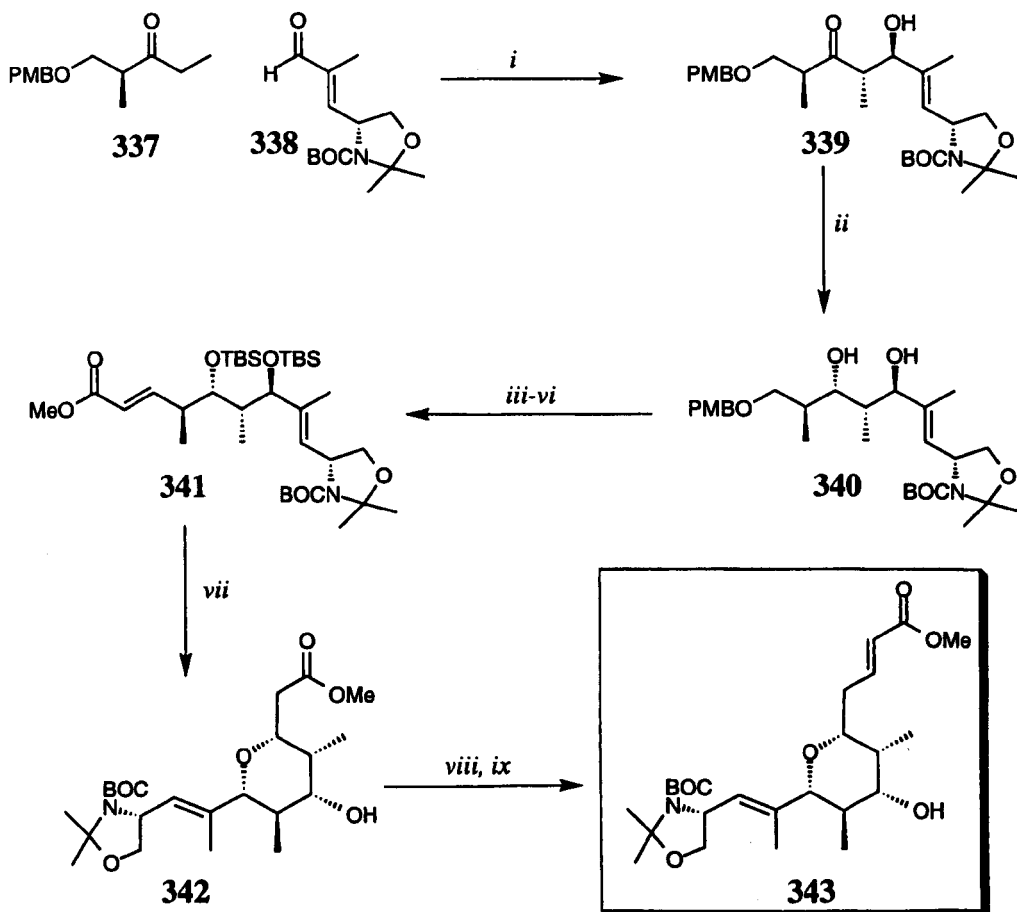
4.1 Contemporaneous Studies

During the course of the research described within this thesis, synthetic work towards phorboxazole A (**4**) was being undertaken by Forsyth *et al*¹⁵⁰ which culminated in a total synthesis of phorboxazole A,^{150d} published in July 1998. This section is intended to be a brief overview of the work of Forsyth's research group and not a rigorous account, for contrast and comparison with our own synthetic efforts to date.

The approach of Forsyth and co-workers was indeed similar to our own. Disconnection of phorboxazole A (**4**) gave three key fragments, the C3-C17 *bis*-pyran unit (**336**), the C18-C30 central pyran unit (**335**) and the C31-C46 side chain (**334**). The major difference in Forsyth's approach was to make use of the 2,4-disubstituted oxazole units for the assembly of these fragments, with macrocyclisation being viewed in a similar light to our strategy *via* an olefination reaction (**Scheme 95**). **Schemes 96, 97** and **98** show Forsyth's approach towards the C18-C30 central pyran unit (**335**),^{150a} the C3-C17 *bis*-pyran unit (**336**),^{150b} and the C31-C46 side chain (**334**)^{150c} respectively. Finally **schemes 99** and **100** show the assembly of these fragments and the completion of the first total synthesis of phorboxazole A.^{150d}

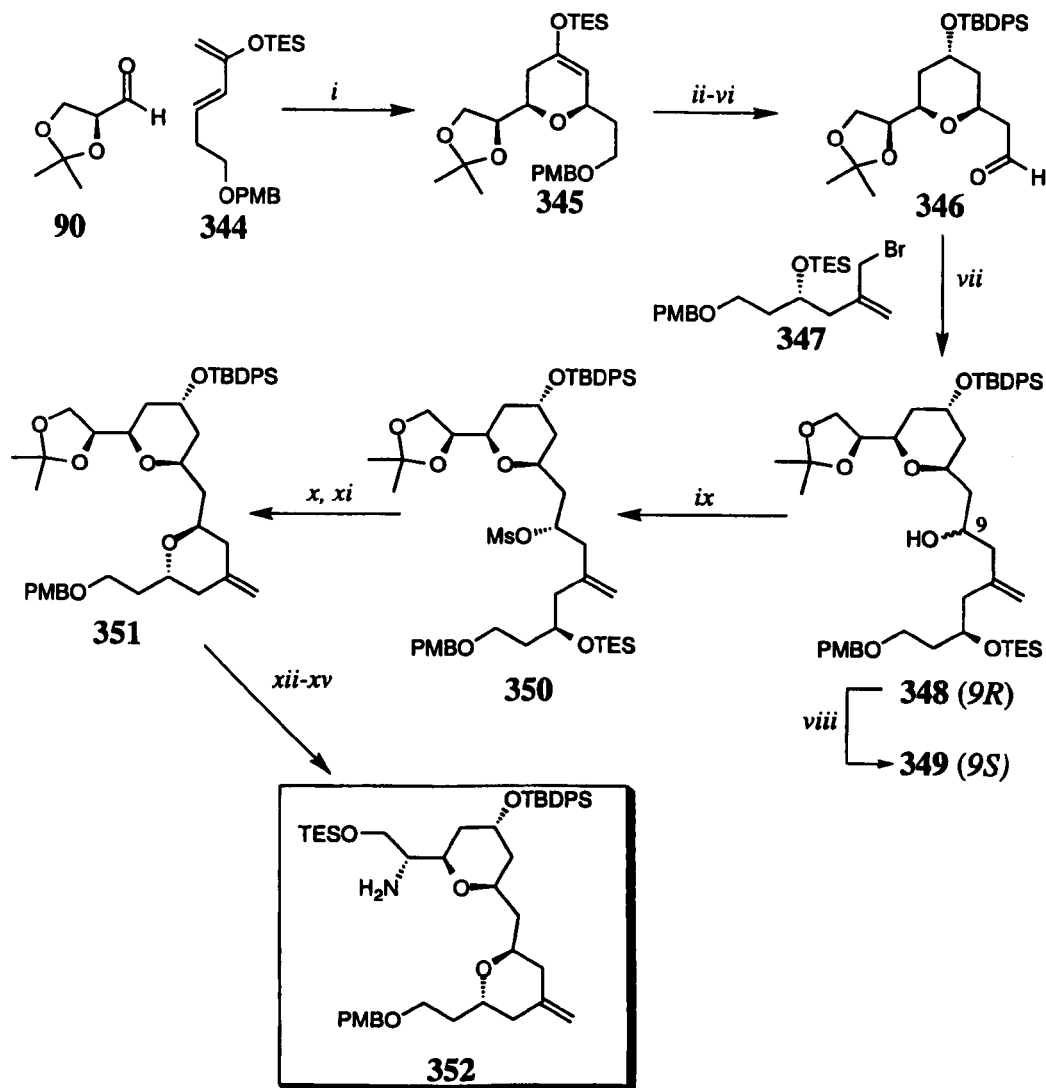


Scheme 95



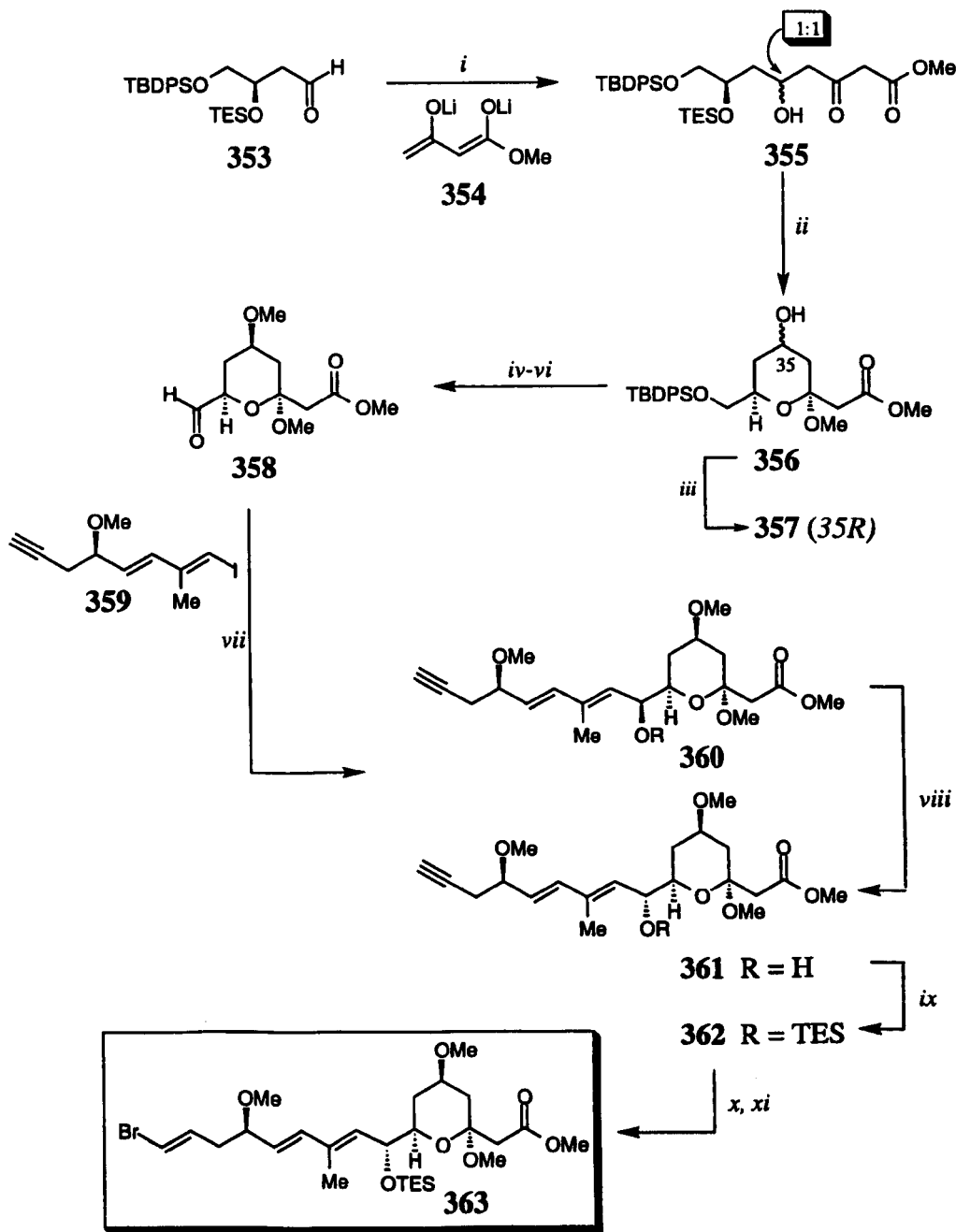
Reagents: i, a) (c-C₆H₁₁)₂BCl, Et₃N, CH₂Cl₂; b) 338, 66%; ii, Me₄NBH(OAc)₃, CH₃CN, AcOH, 97%; iii, TBS-OTf, Et₃N, CH₂Cl₂; iv, DDQ, CH₂Cl₂; v, Dess-Martin periodinane, CH₂Cl₂, 77% (3 steps); vi, Ph₃PCHCO₂Me, CH₃CN, 96%; vii, TBAF, THF, 46%; viii, DIBAL-H, CH₂Cl₂; ix, Ph₃PCHCO₂Me, CH₃CN, 70% (2 steps).

Scheme 96



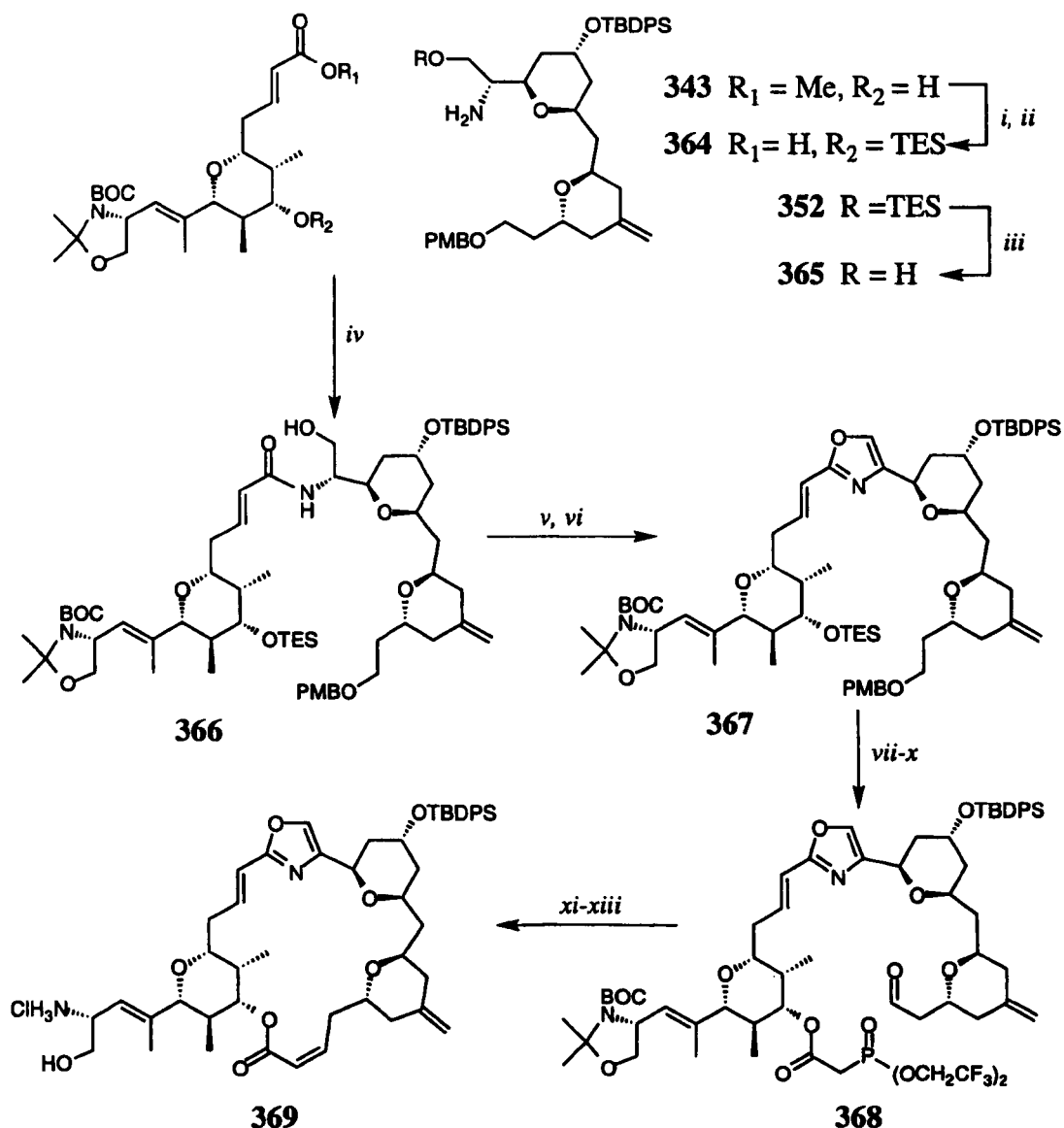
Reagents: *i*, $\text{BF}_3 \cdot \text{OEt}_2$, Et_2O ; *ii*, TBAF, PTSA, THF, 60% (2 steps); *iii*, K-selectride[®], THF, 97%; *iv*, TBDPS-Cl, Et_3N , 93%; *v*, DDQ, CH_2Cl_2 , 97%; *vi*, Dess-Martin periodinane, 80%; *vii*, **347**, $\text{CrCl}_2/\text{NiCl}_2$ (1% w/w), THF, 80% (**349**:**348** 3:2); *viii*, *a\text{PPh}_3, DEAD; *b\text{K}_2\text{CO}_3, MeOH, 76% (2 steps); *ix*, MsCl, Et_3N , CH_2Cl_2 , 96%; *x*, TBAF, 94%; *xi*, Et_3N , CH_3CN , 86%; *xii*, PTSA, MeOH, 97%; *xiii*, TES-Cl, Im., 83%; *xiv*, $(\text{PhO})_2\text{PON}_3$, PPh_3 , DEAD; *xv*, PPh_3 , H_2O , THF, 77% (2 steps).**

Scheme 97



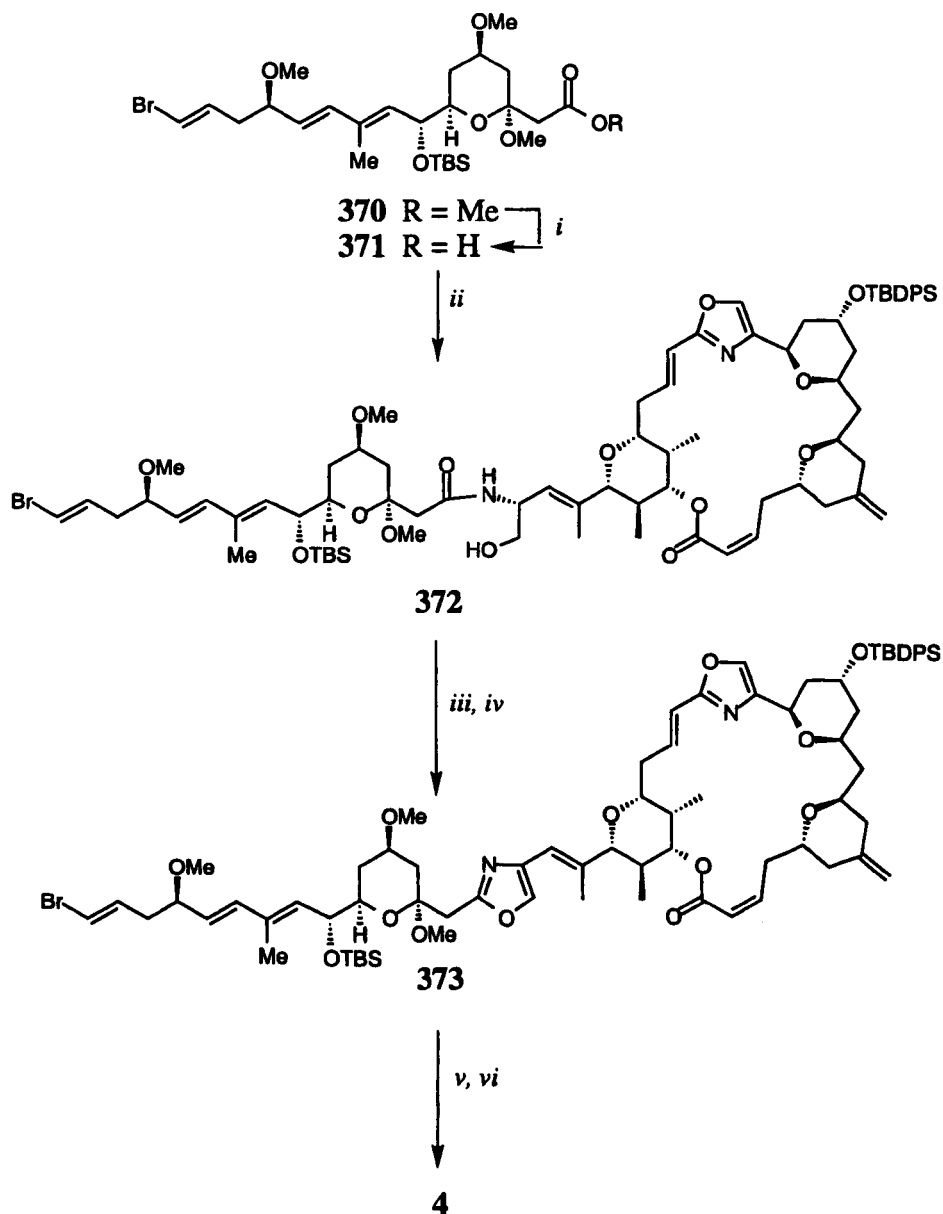
Reagents: *i*, 354, THF; *ii*, PTSA, MeOH, CH₂Cl₂, 50% (2 steps); *iii*, *a*) PNBA, PPh₃, DIAD; *b*) K₂CO₃, MeOH, 76% (2 steps); *iv*, MeI, Ag₂O, CaSO₄, CH₃CN, 80%; *v*, TBAF, THF; *vi*, Dess-Martin periodinane, 81% (2 steps); *vii*, 359, CrCl₂/NiCl₂ (1% w/w), DMSO, 60% (356:357 3:1); *viii*, *a*) PNBA, PPh₃, DIAD; *b*) K₂CO₃, MeOH; *ix*, TES-Cl, Im., DMAP, CH₂Cl₂, 78%; *x*, *n*Bu₃SnH, AIBN, C₆H₆; *xi*, NBS, CH₃CN, 70% (2 steps).

Scheme 98



Reagents: i, TES-Cl, Et₃N; ii, LiOH, H₂O; iii, TBAF, THF; iv, EDC, HOBT, CH₂Cl₂, 87%; v, Dess-Martin periodinane; vi, a) BrCl₂CCl₂Br, PPh₃, 2,6-di-*tert*-butyl-4-methylpyridine, CH₂Cl₂; b) DBU, CH₃CN, 77% (3 steps); vii, TBAF, THF, 94%; viii, HO₂CCH₂PO(OCH₂CF₃)₂, EDC, HOBT, 86%; ix, DDQ, 87%; x, Dess-Martin periodinane, 96%; xi, K₂CO₃, 18-C-6, toluene, 77%, 4:1 *Z:E*; xii, a) PTSA, MeOH, b) chromatography, 77%; xiii, HCl, dioxane.

Scheme 99



Reagents: i, Ba(OH)₂, H₂O, THF, 90%; ii, **369**, EDC, DIPEA, DMAP, CH₂Cl₂, 66%;
 iii, Dess-Martin periodinane; iv, a) BrCl₂CCCl₂Br, PPh₃, 2,6-di-*tert*-butyl-4-methylpyridine, CH₂Cl₂; b) DBU, CH₃CN, 33% (3 steps); v, TBAF, EtOAc; vi, 6% aq. HCl, THF, 74% (2 steps).

Scheme 100

5. REFERENCES

1. Information retrieved from the Internet Homepages of the National Cancer Institute (<http://www.nci.nih.gov>) and of the Institute of Cancer Research (<http://www.icr.ac.uk>).
2. (a) Wani, M.C., Wall, M.E., Taylor, H.L., *J. Am. Chem. Soc.*, **1971**, *93*, 2325; (b) Wall, M.E., Wani, M.C., *J. Ethnopharmacology*, **1996**, *51*, 239.
3. (a) Schiff, P.B., Fant, J., Horwitz, S.B., *Nature*, **1979**, *22*, 665; (b) Manfredi, J.J., Horwitz, S.B., *Pharmacol. Ther.*, **1984**, *25*, 83.
4. Nicolaou, K.C., Riemer, C., Kerr, M., Rideout, D., Wrasidle, W., *Nature*, **1993**, *364*, 464.
5. (a) Hofle, G., Bedorf, N., Gerth, K., Reichenbach, H., (GBF), DE-B 4138042, **1993** [*Chem. Abstr.*, **1993**, *120*, 52841]; (b) Hofle, G., Bedorf, N., Steinmetz, H., Schomburg, D., Gerth, K., Reichenbach, H., *Angew. Chem. Int. Ed.*, **1996**, *35*, 1567.
6. Bollag, D.M., McQueney, P.A., Zhu, J., Hensens, O., Koupal, L., Liesch, J., Goetz, M., Lazarides, E., Woods, C.M., *Cancer Res.*, **1995**, *55*, 2325.
7. (a) Balog, A., Meng, D., Kamenecka, T., Bertinato, P., Su, D.S., Sorensen, E.J., Danishefsky, S.J., *Angew. Chem. Int. Ed.*, **1996**, *35*, 2801; (b) Su, D.S., Meng, D., Bertinato, P., Balog, A., Sorensen, E.J., Danishefsky, S.J., Zheng, Y.H., Chou, T.C., He, L., Horwitz, S.B., *Angew. Chem. Int. Ed.*, **1997**, *36*, 757; (c) Nicolaou, K.C., He, Y., Vourloumis, D., Vallberg, H., Roschangar, F., Sarabia, F., Ninkovic, S., Yang, Z., Trujillo, J.I., *J. Am. Chem. Soc.*, **1997**, *119*, 7960; (d) Yang, Z., He, Y., Vourloumis, D., Vallberg, H., Nicolaou, K.C., *Angew. Chem. Int. Ed.*, **1997**, *36*, 166; (e) Nicolaou, K.C., Ninkovic, S., Sarabia, F., Vourloumis, D., He, Y., Vallberg, H., Finlay, M.R.V., Yang, Z., *J. Am. Chem. Soc.*, **1997**, *119*, 7974; (f) Schinzer, D., Limberg, A., Bauer, A., Bohm, O.M., Cordes, M., *Angew. Chem. Int. Ed.*, **1997**, *36*, 523.
8. (a) Su, D.S., Balog, A., Meng, D., Bertinato, P., Danishefsky, S.J., Zheng, Y.H., Chou, T.C., He, L., Horwitz, S.B., *Angew. Chem. Int. Ed.*, **1997**,

- 36, 2093; (b) Balog, A., Bertinato, P., Su, D.S., Meng, D., Sorensen, E.J., Danishefsky, S.J., Zheng, Y.H., Chou, T.C., He, L., Horwitz, S.B., *Tetrahedron Lett.*, **1997**, 38, 4529; (c) Nicolaou, K.C., Vourloumis, D., Li, T., Pastor, J., Winssinger, N., He, Y., Ninkovic, S., Sarabia, F., Vallberg, H., Roschangar, F., King, N.P., Finlay, M.R.V., Giannakakou, P., Verdier-Pinard, P., Hamel, E., *Angew. Chem. Int. Ed.*, **1997**, 36, 2097; (d) Nicolaou, K.C., Ninkovic, S., Finlay, M.R.V., Sarabia, F., Li, T., *Chem. Commun.*, **1997**, 2343; (e) Nicolaou, K.C., Sarabia, F., Finlay, M.R.V., Ninkovic, S., King, N.P., Vourloumis, D., He, Y., *Chem. Eur. J.*, **1997**, 3, 1971; (f) Nicolaou, K.C., Sarabia, F., Ninkovic, S., Finlay, M.R.V., Boddy, C.N.C., *Angew. Chem. Int. Ed.*, **1998**, 37, 81.
9. Nicolaou, K.C., Roschangar, F., Vourloumis, D., *Angew. Chem. Int. Ed.*, **1998**, 37, 2014.
 10. (a) Searle, P.A., Molinski, T.F., *J. Am. Chem. Soc.*, **1995**, 117, 8126; (b) Searle, P.A., Molinski, T.F., Brzezinski, L.J., Leahy, J.W., *J. Am. Chem. Soc.*, **1996**, 118, 9422; (c) Molinski, T.F., *Tetrahedron Lett.*, **1996**, 37, 7879.
 11. Rudi, A., Stein, Z., Green, S., Goldberg, L., Kashman, Y., Benayahu, Y., Schleyer, M., *Tetrahedron Lett.*, **1994**, 35, 2589.
 12. (a) Petit, G.R., Cichacz, Z.A., Gao, F., Herald, C.L., Boyd, M.R., Schmidt, J.M., Hooper, J.N.A., *J. Org. Chem.*, **1993**, 58, 1302; (b) Petit, G.R., Cichacz, Z.A., Gao, F., Herald, C.L., Boyd, M.R., *J. Chem. Soc., Chem. Commun.*, **1993**, 1166; (c) Petit, G.R., Cichacz, Z.A., Herald, C.L., Gao, F., Boyd, M.R., Schmidt, J.M., Hamel, E., Bai, R., *J. Chem. Soc., Chem. Commun.*, **1994**, 1605; (d) Bai, R., Taylor, G.F., Cichacz, Z.A., Herald, C.L., Kepler, J.A., Petit, G.R., Hamel, E., *Biochemistry*, **1995**, 34, 9714.
 13. Sullivan, K.F., *Annu. Rev. Cell Biol.*, **1988**, 4, 687.
 14. Gerwick, W.H., Proteau, P.J., Nagle, D.G., Hamel, E., Blokhin, A., Slate, D.L., *J. Org. Chem.*, **1994**, 59, 1243.

15. (a) Iwasaki, S., Kobayashi, H., Furukawa, J., Namikoshi, M., Okuda, S., Sato, Z., Matsuda, I., Noda, T., *J. Antibiotics*, **1984**, *37*, 354; (b) Takahashi, M., Iwasaki, S., Kobayashi, H., Okuda, S., Murai, T., Sato, Y., *Biochim. Biophys. Acta*, **1987**, *926*, 215.
16. Hung, D.T., Chen, J., Schreiber, S.L., *Chem. Biol.*, **1996**, *3*, 287.
17. Lindel, T., Jensen, P.R., Fenical, W., Long, B.H., Casazza, A.M., Carboni, J., Fairchild, C.R., *J. Am. Chem. Soc.*, **1997**, *119*, 8744.
18. (a) D'Ambrosio, M., Guerriero, A., Pietra, F., *Helv. Chim. Acta*, **1987**, *70*, 2019; (b) D'Ambrosio, M., Guerriero, A., Pietra, F., *Helv. Chim. Acta*, **1988**, *71*, 964; (c) Ciomei, M., Albanese, C., Pastori, W., Grandi, M. Pietra, F., D'Ambrosio, M., Guerriero, A., Battistini, C., *Proc. Am. Assoc. Canc. Res.*, **1997**, *38*, 5.
19. (a) Uemura, D., Takahashi, K., Yamamoto, T., Katayama, C., Tanaka, J., Okumura, Y., Hirata, Y., *J. Am. Chem. Soc.*, **1985**, *107*, 4796; (b) Hirata, Y., Uemura, D., *Pure Appl. Chem.*, **1986**, *58*, 701.
20. Aicher, T.D., Buszek, K.R., Fang, F.G., Forsyth, C.J., Jung, S.H., Kishi, Y., Matelich, M.C., Scola, P.M., Spero, D.M., Yoon, S.K., *J. Am. Chem. Soc.*, **1992**, *114*, 3162.
21. (a) Uemura, D., Ueda, K., Hirata, Y., Naoki, H., Iwashita, T., *Tetrahedron Lett.*, **1981**, *22*, 2781; (b) Moore, R.E., Bartolini, G., *J. Am. Chem. Soc.*, **1981**, *103*, 2491.
22. (a) Kishi, Y., *Pure Appl. Chem.*, **1989**, *61*, 313; (b) Suh, E.M., Kishi, Y., *J. Am. Chem. Soc.*, **1994**, *116*, 11205 and references cited therein.
23. (a) Lin, Y.Y., Risk, M.M., Ray, S.M., Van Engen, D., Clardy, J., Golik, J., James, J.C., Nakanishi, K., *J. Am. Chem. Soc.*, **1981**, *103*, 6773; (b) Lee, M.S., Repeta, D.J., Nakanishi, K., Zagorski, M.G., *J. Am. Chem. Soc.*, **1986**, *108*, 7855.
24. Anderson, D.M., *Sci. Am.*, **1994**, *8*, 62 and references cited therein.
25. (a) Nicolaou, K.C., Theodorakis, E.A., Rutjes, F.P.J.T., Tiebes, J., Sato,

- M., Untersteller, E., Xiao, X.Y., *J. Am. Chem. Soc.*, **1995**, *117*, 1171; (b) Nicolaou, K.C., Theodorakis, E.A., Rutjes, F.P.J.T., Tiebes, J., Sato, M., Untersteller, E., *J. Am. Chem. Soc.*, **1995**, *117*, 1173.
26. Fusetani, N., Shinoda, K., Matsunaga, S., *J. Am. Chem. Soc.*, **1993**, *115*, 3977.
 27. (a) Kobashi, M., Aoki, S., Skai, H., Kawazoe, K., Kihara, N., Sasaki, T., Kitogawa, I., *Tetrahedron Lett.*, **1993**, *34*, 2795; (b) Kobashi, M., Aoki, S., Skai, H., Kihara, N., Sasaki, T., Kitogawa, I., *Chem. Pharm. Bull.*, **1993**, *41*, 989; (c) Kobashi, M., Aoki, S., Kitogawa, I., *Tetrahedron Lett.*, **1994**, *35*, 1243.
 28. (a) Evans, D.A., Coleman, P.J., Dias, L.C., *Angew. Chem. Int. Ed.*, **1997**, *36*, 2738; (b) Evans, D.A., Trotter, B.W., Côté, B., Coleman, P.J., *Angew. Chem. Int. Ed.*, **1997**, *36*, 2741; (c) Evans, D.A., Trotter, B.W., Côté, B., Coleman, P.J., Dias, L.C., Tyler, A.N., *Angew. Chem. Int. Ed.*, **1997**, *36*, 2744.
 29. (a) Guo, J., Duffy, K.J., Stevens, K.L., Dalko, P.I., Roth, R.M., Hayward, M.M., Kishi, Y., *Angew. Chem. Int. Ed.*, **1998**, *37*, 187; (b) Guo, J., Duffy, K.J., Stevens, K.L., Dalko, P.I., Roth, R.M., Hayward, M.M., Kishi, Y., *Angew. Chem. Int. Ed.*, **1998**, *37*, 192.
 30. Kato, Y., Fusetani, N., Matsunaga, S., Hashimoto, K., Fujita, S., Furuya, T., *J. Am. Chem. Soc.*, **1986**, *108*, 2780.
 31. Ishibara, H., Martin, B.L., Brautigan, D.L., Karaki, H., Ozaki, H., Kato, Y., Fusetani, N., Watabe, S., Hashimoto, K., Uemura, D., Hartshorne, D.J., *Biochem. Biophys. Res. Commun.*, **1989**, *159*, 871.
 32. Evans, D.A., Gage, J.R., Leighton, J.L., *J. Am. Chem. Soc.*, **1992**, *114*, 9434.
 33. Tanimoto, N., Gerritz, S.W., Sawabe, A., Noda, T., Filla, S.A., Masamune, S., *Angew. Chem. Int. Ed.*, **1994**, *33*, 673.
 34. Yokokawa, F., Hamada, Y., Shioiri, T., *Chem. Commun.*, **1996**, 871.

35. Brazhnikova, M.G., Kudinova, M.K., Potapova, N.P., Filippova, T.M., Borowski, E., Zelinski, Y., Golik, J., *Bioorgan. Khim.*, **1976**, 2, 149.
36. Tavares, F., Lawson, J.P., Meyers, A.I., *J. Am. Chem. Soc.*, **1996**, 118, 3303.
37. Delpierre, G.R., Eastwood, F.W., Gream, G.E., Kingston, D.G.I., Lord Todd, A.R., Williams, D.H., *J. Chem. Soc. C*, **1966**, 1653.
38. Schlessinger, R.H., Li, Y.J., *J. Am. Chem. Soc.*, **1996**, 118, 3301.
39. (a) Entwistle, D.A., Jordon, S.I., Montgomery, J., Pattenden, G., *J. Chem. Soc., Perkin Trans. 1*, **1996**, 315; (b) Entwistle, D.A., Jordon, S.I., Montgomery, J., Pattenden, G., *Synthesis*, **1998**, 603.
40. Kobayashi, J., Kondo, K., Ishibashi, M., Walchli, M.R., Nakamura, T., *J. Am. Chem. Soc.*, **1993**, 115, 6661.
41. (a) Jansen, R., Kunze, B., Wray, V., Reichenbach, H., Juriewicz, E., Hunsmann, G., Holfe, G., *Liebigs Ann. Chem.*, **1991**, 707; (b) Kunze, B., Jansen, R., Pridzun, L., Juriewicz, E., Hunsmann, G., Holfe, G., Reichenbach, H., *J. Antibiotics*, **1992**, 45, 1549.
42. (a) Ishibashi, Y., Ohba, S., Nishiyama, S., Yamamura, S., *Tetrahedron Lett.*, **1996**, 37, 2997; (b) Garey, D., Ramirez, M., Gonzales, S., Wertsching, A., Tith, S., Keefe, K., Pena, M.R., *J. Org. Chem.*, **1996**, 61, 4853.
43. Burke, S.D., Hong, J., Lennox, J.R., Mongin, A.P., *J. Org. Chem.*, **1998**, 63, 6952 and references cited therein.
44. (a) Pattenden, G., *J. Heterocyclic Chem.*, **1992**, 29, 607; (b) Faulkner, D.J., *Nat. Prod. Rep.*, **1998**, 15, 113; (c) Lewis, J.R., *Nat. Prod. Rep.*, **1998**, 15, 371.
45. Michael, J.P., Pattenden, G., *Angew. Chem. Int. Ed.*, **1993**, 32, 1.
46. Admi, V., Afek, U., Carmeli, S., *J. Nat. Prod.*, **1996**, 59, 396.
47. Freeman, D.J., Pattenden, G., *Tetrahedron Lett.*, **1998**, 39, 3251.
48. Nagatsu, A., Kajitani, H., Sakakibara, J., *Tetrahedron Lett.*, **1995**, 36, 4097.
49. Wipf, P., Venkatraman, S., *J. Org. Chem.*, **1996**, 61, 6517.

50. Muir, J.C., Pattenden, G., Thomas, R.M., *Synthesis*, **1998**, 613.
51. Lindquist, N., Fenical, W., Van Duyne, G.D., Clardy, J., *J. Am. Chem. Soc.*, **1991**, *113*, 2303.
52. Ichiba, T., Yoshida, W.Y., Scheuer, P.J., Higa, T., Gravalos, D.G., *J. Am. Chem. Soc.*, **1991**, *113*, 3173.
53. (a) Wipf, P., Lim, S., *J. Am. Chem. Soc.*, **1995**, *117*, 558; (b) Wipf, P., Lim, S., *Chimia*, **1996**, *50*, 157.
54. Roesener, J.A., Scheuer, P.J., *J. Am. Chem. Soc.*, **1986**, *108*, 846.
55. (a) Kernan, M.R., Molinski, T.F., Faulkner, D.J., *J. Org. Chem.*, **1988**, *53*, 5014; (b) Matsunaga, S., Fusetani, N., Hashimoto, K., Koseki, K., Noma, M., Noguchi, H., Sankawa, U., *J. Org. Chem.*, **1989**, *54*, 1360.
56. Matsunaga, S., Fusetani, N., Hashimoto, K., Koseki, K., Noma, M., *J. Am. Chem. Soc.*, **1986**, *108*, 847.
57. Fusetani, N., Yasumuro, K., Matsunaga, S., Hashimoto, K., *Tetrahedron Lett.*, **1989**, *30*, 2809.
58. Chattopadhyay, S.K., Pattenden, G., *Tetrahedron Lett.*, **1998**, *39*, 6095.
59. Ohtani, I., Kusumi, T., Kashman, Y., Kakisawa, H., *J. Am. Chem. Soc.*, **1991**, *113*, 4092.
60. Still, W.C., Gennari, C., *Tetrahedron Lett.*, **1983**, *24*, 4495.
61. (a) Pattenden, G., Thom, S.M., *Synlett*, **1993**, 215; (b) Boden, C.D.J., Pattenden, G., *Synlett*, **1994**, 181; (c) Boyce, R.J., Pattenden, G., *Tetrahedron Lett.*, **1996**, *37*, 3501; (d) Critcher, D., Pattenden, G., *Tetrahedron Lett.*, **1996**, *37*, 9107.
62. Pattenden, G., Ye, T., *Tetrahedron Lett.*, **1998**, *39*, 319.
63. Diels, O., Alder, K., *Justus Liebigs Ann. Chem.*, **1928**, 460, 98.
64. (a) Boger, D.L., Weinreb, S.M., *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic Press Inc., New York, **1987**; (b) Boger, D.L. In *Comprehensive Organic Synthesis*; Trost, B.M., Fleming, I., Eds., Pergamon Press, Oxford; **1991**, Vol. 5, pp 451-512.

65. (a) Dale, W.J., Sisti, A.J., *J. Org. Chem.*, **1957**, *22*, 449; (b) Shavrygina, O.A., Makin, S.M., *Zh. Org. Khim.*, **1966**, *2*, 1354; (c) Smushkevich, Y.I., Belov, V.N., Kleev, B.V., Akimova, A.Y., *Zh. Org. Khim.*, **1967**, *3*, 1036.
66. Begley, M.J., Benner, J.P., Gill, G.B., *J. Chem. Soc., Perkin Trans. 1*, **1981**, 1112.
67. Jurczak, J., Chmielewski, M., Filipek, S., *Synthesis*, **1979**, 41.
68. Jurczak, J., Bauer, T., Filipek, S., Tkacz, M., Zygo, K., *J. Chem. Soc., Chem. Commun.*, **1983**, 540.
69. (a) Danishefsky, S.J., Kerwin, J.F., Jr., Kobayashi, S., *J. Am. Chem. Soc.*, **1982**, *104*, 358; (b) Danishefsky, S.J., Kerwin, J.F., Jr., *J. Org. Chem.*, **1982**, *47*, 3183; (c) Danishefsky, S.J., Webb, R.R., *J. Org. Chem.*, **1984**, *49*, 1955.
70. (a) Larsen, E.R., Danishefsky, S.J., *J. Am. Chem. Soc.*, **1982**, *104*, 6458; (b) Larsen, E.R., Danishefsky, S.J., *Tetrahedron Lett.*, **1982**, *23*, 1975; (c) Danishefsky, S.J., Larsen, E.R., Askin, D., Kato, N., *J. Am. Chem. Soc.*, **1985**, *107*, 1246.
71. (a) Danishefsky, S.J., Kato, N., Askin, D., Kerwin, J.F., Jr., *J. Am. Chem. Soc.*, **1982**, *104*, 360; (b) Danishefsky, S.J., Larsen, E.R., Askin, D., *J. Am. Chem. Soc.*, **1982**, *104*, 6457; (c) Danishefsky, S.J., Kobayashi, S., Kerwin, J.F., Jr., *J. Org. Chem.*, **1982**, *47*, 1981; (d) Bednarski, M., Danishefsky, S.J., *J. Am. Chem. Soc.*, **1983**, *105*, 6968; (e) Danishefsky, S.J., Pearson, W.H., Harvey, D.F., *J. Am. Chem. Soc.*, **1984**, *106*, 2455; (f) Danishefsky, S.J., Pearson, W.H., Harvey, D.F., Maring, C.J., Springer, J.P., *J. Am. Chem. Soc.*, **1985**, *107*, 1256.
72. (a) Danishefsky, S.J., Maring, C.J., *J. Am. Chem. Soc.*, **1985**, *107*, 1269; (b) Danishefsky, S.J., Larsen, E.R., Springer, J.P., *J. Am. Chem. Soc.*, **1985**, *107*, 1274; (c) Danishefsky, S.J., Pearson, W.H., Segmuller, B.E., *J. Am. Chem. Soc.*, **1985**, *107*, 1280; (d) Danishefsky, S.J., Uang, B.J., Quallich, G., *J. Am. Chem. Soc.*, **1985**, *107*, 1285 (e) Danishefsky, S.J.,

- Maring, C.J., *J. Am. Chem. Soc.*, **1985**, *107*, 7762 and references cited therein.
73. (a) Mujica, M.T., Afonso, M.M., Galindo, A., Palenzuela, J.A., *Tetrahedron Lett.*, **1994**, *35*, 3401; (b) Mujica, M.T., Afonso, M.M., Galindo, A., Palenzuela, J.A., *Synlett*, **1996**, 983.
74. Meng, D., Bertinato, P., Balog, A., Su, D.S., Kamenecka, T., Sorensen, E.J., Danishefsky, S.J., *J. Am. Chem. Soc.*, **1997**, *119*, 10073.
75. (a) Meng, D., Sorensen, E.J., Bertinato, P., Danishefsky, S.J., *J. Org. Chem.*, **1996**, *61*, 7998; (b) Meng, D., Sorensen, E.J., Bertinato, P., Danishefsky, S.J., *J. Org. Chem.*, **1996**, *61*, 8000.
76. Waldmann, H., *Synthesis*, **1994**, 535 and references cited therein.
77. (a) Bednarski, M., Danishefsky, S.J., *J. Am. Chem. Soc.*, **1983**, *105*, 3716; (b) Bednarski, M., Maring, C., Danishefsky, S.J., *Tetrahedron Lett.*, **1983**, *24*, 3451.
78. (a) Evans, D.A., Johnson, J.S., *J. Am. Chem. Soc.*, **1998**, *120*, 4895; (b) Schaus, S.E., Brånalt, J., Jacobsen, E.N., *J. Org. Chem.*, **1998**, *63*, 403 and references cited therein.
79. Cornforth, J. W., Cornforth, R. H., *J. Chem. Soc.*, **1947**, 96.
80. Meyers, A. I., Lawson, J. P., *Tetrahedron Lett.*, **1981**, *22*, 3163.
81. Danishefsky, S.J., Yan, C.F., Singh, R.K., Gammill, R.B., McCurry, P.M., Jr., Fritsch, N., Clardy, J., *J. Am. Chem. Soc.*, **1979**, *101*, 7001.
82. Posner, G.H., *Org. React.*, **1972**, *19*, 1.
83. Palenzuela, J.A., Galindo, A., Afonso, M.M., Mujica, M.T., *Tetrahedron*, **1996**, *52*, 2167.
84. Grieco, P.A., Moher, E.D., *Tetrahedron Lett.*, **1993**, *34*, 5567.
85. (a) Garner, P., Park, J.M., *J. Org. Chem.*, **1987**, *52*, 2361; (b) Garner, P., Park, J.M., *Organic Synthesis*, **1991**, *70*, 18.
86. Lafargue, P., Guenot, P., Lellouche, J.P., *Heterocycles*, **1995**, *41*, 947.
87. Meyers, A.I., Novacheck, K.A., *Tetrahedron Lett.*, **1996**, *37*, 1743.

88. Mancuso, A.J., Huang, S-L., Swern, D., *J. Org. Chem.*, **1978**, *43*, 2480.
89. Parikh, J.R., Doering, W.von E., *J. Am. Chem. Soc.*, **1967**, *89*, 5505.
90. Dess, D.B., Martin, J.C., *J. Am. Chem. Soc.*, **1991**, *113*, 7277.
91. McKillop, A., Taylor, R.J.K., Watson, R.J., Lewis, N., *Synthesis*, **1994**, 31.
92. For a review on the occurrence and chemistry of oxazoles see "Oxazoles"; Turchi, I.J., Ed.; Wiley, New York, **1986** and other reviews cited therein.
93. Meyers, A.I., Knaus, G., Kamata, K., Ford, M.E., *J. Am. Chem. Soc.*, **1976**, *98*, 567.
94. (a) Doyle, M.P., Buhro, W.E., Davidson, J.G., Elliot, R.C., Hoekstra, J.W., Oppenhuizen, M., *J. Org. Chem.*, **1980**, *45*, 3657; (b) Connell, R.D., Tebbe, M., Gangloff, A.R., Helquist, P., *Tetrahedron*, **1993**, *49*, 4555 and references cited therein.
95. Konopelski, J.P., Hottenroth, J.M., Oltra, H.M., Véliz, E.A., Yang, Z-C., *Synlett*, **1996**, 609.
96. (a) Lakhan, R., Ternai, B., *Adv. Heterocycl. Chem.*, **1974**, *17*, 99; (b) Vaccaro, H., Levy, D.E., Sawade, A., Jaetsch, T., Masamune, S., *Tetrahedron Lett.*, **1992**, *33*, 1937.
97. Aguilar, E., Meyers, A.I., *Tetrahedron Lett.*, **1994**, *35*, 2473.
98. Panek, J.S., Beresis, R.T., *J. Org. Chem.*, **1996**, *61*, 6496.
99. Hamada, Y., Shibata, M., Shioira, T., *Tetrahedron Lett.*, **1985**, *26*, 6501.
100. Misra, R.N., Brown, B.R., Sher, P.M., Patel, M.M., Hall, S.F., Han, W-C., Barrish, J.C., Kocy, O., Harris, D.N., Goldenberg, H.J., Michael, I.M., Schumacher, W.A., Webbs, M.L., Monshizadegan, H., Ogletree, M.L., *J. Med. Chem.*, **1993**, *36*, 1401.
101. Galéotti, N., Montagne, C., Poncet, J., Jouin, P., *Tetrahedron Lett.*, **1996**, *33*, 2807.
102. Dahuron, N., Langois, N., Chiaroni, A., Riche, C., *Heterocycles*, **1996**, *142*, 635.

103. Atkins, G.M., Burgess, E.M., *J. Am. Chem. Soc.*, **1968**, *90*, 4744.
104. Wipf, P., Miller, C.P., *Tetrahedron Lett.*, **1992**, *33*, 907.
105. Evans, D.L., Minster, D.K., Jordis, U., Hecht, S.M., Mazzu, A.L., Jr., Meyers, A.I., *J. Org. Chem.*, **1979**, *44*, 497.
106. Barrish, J.C., Singh, J., Spergel, S.H., Han, W.C., Kissick, T.P., Kronenthal, D.R., Mueller, R.H., *J. Org. Chem.*, **1993**, *58*, 4494.
107. Meyers, A.I., Tavares, F., *Tetrahedron Lett.*, **1994**, *35*, 6803.
108. Evans, D.A., Gage, J.R., Leighton, J.L., Kim, A.S., *J. Org. Chem.*, **1992**, *57*, 1961.
109. Videnov, G., Kaiser, D., Kempter, C., Jung, G., *Angew. Chem. Int. Ed.*, **1996**, *35*, 1503.
110. Williams, D.R., Lowder, P.D., Gu, Y-G., Brooks, D.A., *Tetrahedron Lett.*, **1997**, *38*, 331.
111. Wipf, P., Miller, C.P., *J. Org. Chem.*, **1993**, *58*, 3604.
112. Blanchette, M.A., Choy, W., Davis, J.T., Essinfeld, A.P., Masamune, S., Roush, W.R., Sakai, T., *Tetrahedron Lett.*, **1984**, *25*, 2183.
113. Tkaczuk, P., Thornton, E.R., *J. Org. Chem.*, **1981**, *46*, 4393.
114. Banwell, M.G., Bui, C.T., Pham, H.T.T., Simpson, G.W., *J. Chem. Soc., Perkin Trans. 1*, **1996**, 967.
115. Edmunds, A.J.F., Trueb, W., *Tetrahedron Lett.*, **1997**, *38*, 1009.
116. (a) Brown, H.C., Jadhav, P.K., *J. Am. Chem. Soc.*, **1983**, *105*, 2092; (b) Brown, H.C., Randad, R.S., Bhat, K.S., Zaidlewicz, M., Racherla, U.S., *J. Am. Chem. Soc.*, **1990**, *112*, 2389; (c) Brown, H.C., Ramachandran, P.V., *J. Organomet. Chem.*, **1995**, *500*, 1.
117. (a) Dale, J.A., Dull, D.L., Mosher, H.S., *J. Org. Chem.*, **1969**, *34*, 2543; (b) Dale, J.A., Mosher, H.S., *J. Am. Chem. Soc.*, **1973**, *95*, 512.
118. (a) Rychnovsky, S.D., Skalitzky, D.J., *Tetrahedron Lett.*, **1990**, *31*, 945; (b) Rychnovsky, S.D., Rogers, B.N., Richardson, T.I., *Acc. Chem. Res.*, **1998**, *31*, 9.

119. Evans, D.A., Rieger, D.L., Gage, J.R., *Tetrahedron Lett.*, **1990**, *31*, 7099.
120. Lewis, M.D., Cha, J.K., Kishi, Y., *J. Am. Chem. Soc.*, **1982**, *104*, 4976.
121. (a) Paterson, I., Cumming, J.G., *Tetrahedron Lett.*, **1992**, *33*, 2847; (b) Paterson, I., Cumming, J.G., Ward, R.A., Lambole, S., *Tetrahedron*, **1995**, *51*, 9393; (c) Richter, P.K., Tomaszewski, M.J., Miller, R.A., Patron, A.P., Nicolaou, K.C., *J. Chem. Soc., Chem. Commun.*, **1994**, 1151.
122. Hosomi, A., Sakata, Y., Sakurai, H., *Tetrahedron Lett.*, **1984**, *25*, 2383.
123. Gray, G.R., Wong, M.Y.H., *J. Am. Chem. Soc.*, **1978**, *100*, 3548.
124. White, J.D., Jensen, M.S., *J. Am. Chem. Soc.*, **1995**, *117*, 6224.
125. Smith, A.B., Condon, S.M., McCauley, J.A., Leazer, J.L., Jr., Leahy, J.W., Maleczka, R.E., Jr., *J. Am. Chem. Soc.*, **1997**, *119*, 947 and references cited therein.
126. Evans, D.A., Truesdale, L.K., Grimm, K.G., Nesbitt, S.L., *J. Am. Chem. Soc.*, **1977**, *99*, 5009.
127. (a) Oppong, I., Pauls, H.W., Liang, D., Fraser-Reid, B., *J. Chem. Soc., Chem. Commun.*, **1986**, 1241; (b) Konishita, M., Taniguchi, M., Morioka, M., Takami, H., Mizusawa, Y., *Bull. Chem. Soc. Jpn.*, **1988**, *61*, 2147; (c) De Brabander, J., Vandewalle, M., *Synthesis*, **1994**, 855.
128. Julia, M., Paris, J.M., *Tetrahedron Lett.*, **1973**, *14*, 4833.
129. (a) Baudin, J.B., Hareau, G., Julia, S.A., Ruel, O., *Tetrahedron Lett.*, **1991**, *32*, 1175; (b) Baudin, J.B., Hareau, G., Julia, S.A., Ruel, O., *Bull. Soc. Chim. Fr.*, **1993**, *130*, 336; (c) Baudin, J.B., Hareau, G., Julia, S.A., Lorne, R., Ruel, O., *Bull. Soc. Chim. Fr.*, **1993**, *130*, 856.
130. Kocienski, P.J., Smith, N.D., Street, S.D.A., *Synthesis*, **1996**, 652.
131. Bellingham, R., Jarowicki, K., Kocienski, P.J., Martin, V., *Synthesis*, **1996**, 285.
132. Blakemore, P.R., Cole, W.J., Kocienski, P.J., Morley, A., *Synlett*, **1998**, 26.
133. Oikawa, Y., Yoshioka, T., Yonemitsu, O., *Tetrahedron Lett.*, **1982**, *23*, 885.

134. (a) Hilbert, P., Marmor, R.S., Seyferth, D., *J. Org. Chem.*, **1971**, *36*, 1379;
(b) Gilbert, J.C., Weerasooriya, U., *J. Org. Chem.*, **1979**, *44*, 4997.
135. Guindon, Y., Yoakim, C., Morton, H.E., *J. Org. Chem.*, **1984**, *49*, 3912.
136. Holmquist, C.R., Roskamp, E.J., *J. Org. Chem.*, **1989**, *54*, 3258.
137. Pattenden, G., Plowright, A.T., Tornos, J.A., Ye, T., *Tetrahedron Lett.*, **1998**, *39*, 6099.
138. Nomura, K., Iida, T., Hori, K., Yoshii, E., *J. Org. Chem.*, **1994**, *59*, 488.
139. Ireland, R.E., Liu, L., *J. Org. Chem.*, **1993**, *58*, 2899.
140. Garey, D., Ramirez, M., Gonzales, S., Wertsching, A., Tith, S., Keefe, K., Peña, M., *J. Org. Chem.*, **1996**, *61*, 4853.
141. Boger, D.L., Curran, T., *J. Org. Chem.*, **1992**, *57*, 2235.
142. Lygo, B., *Tetrahedron*, **1988**, *44*, 6889.
143. Kusakabe, M., Kato, H., Sato, F., *Chem. Lett.*, **1987**, 2163.
144. Kraus, G.A., Nagy, J.O., *Tetrahedron Lett.*, **1983**, *24*, 3427.
145. Meguro, K., Tawada, K., Sugiyama, Y., Fujita, T., Kawamatsu, Y., *Chem. Pharm. Bull.*, **1986**, *34*, 2840.
146. McNulty, J., Still, I.W.J., *Synth. Commun.*, **1992**, *22*, 979.
147. Boeckman, R.K. Jr., Charette, A.B., Asberom, T., Johnston, B.H., *J. Am. Chem. Soc.*, **1987**, *109*, 7553.
148. Roush, W.R., Hoong, L.K., Palmer, M.A.J., Straub, J.A., Palkowitz, A.D., *J. Org. Chem.*, **1990**, *55*, 4117.
149. Lance, D.G., Jones, J.K.N., *Can. J. Chem.*, **1967**, *45*, 1533.
150. (a) Lee, C.S., Forsyth, C.J., *Tetrahedron Lett.*, **1996**, *37*, 6449; (b) Cink, R.D., Forsyth, C.J., *J. Org. Chem.*, **1997**, *62*, 5672; (c) Ahmed, F., Forsyth, C.J., *Tetrahedron Lett.*, **1998**, *39*, 183; (d) Forsyth, C.J., Ahmed, F., Cink, R.D., Lee, C.S., *J. Am. Chem. Soc.*, **1998**, *120*, 5597.